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Master's Thesis

Strategies to improve solubility and dissolution of Pranlukast

프란루카스트의 용해도와 용출 향상을 위한 전략

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Advisor: Professor Hoo-Kyun Choi

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Department of Pharmacy

Taksim Ahmed

Taksim Ahmed's thesis is examined and approved for the Master's degree

Committee Chairperson ----------
Prof. Choi, Hong Seok, Chosun University.

Committee Member ----------
Prof. Oh, Won Keun, Chosun University.

Committee Member ----------
Prof. Choi, Hoo Kyun, Chosun University.

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Graduate School of Chosun University

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아흐메드 탁심

지도교수 : 최후균

조선대학교 대학원 약학과

이 실험의 목적은 난용성 약물인 Pranlukast의 용해도와 용출을 높이는 것이었다. Pranlukast와 Kollidon® VA64가 1:2 의 질량 비로 이루어진 고체분산체(SD)를 용매 증발법으로 제조하였으며, 같은 구성으로 이루어진 단순혼합물(PM)을 대조실험을 위해 만들었다. SD의 경우, Differential scanning calorimeter와 X-ray diffraction에서 pranlukast의 부분적인 결정구조가 관찰되었다. SD와 PM 제형의 carrier로서 다양한 친수성 고분자를 조사한 결과 PH 6.8에서 Kollidon® VA64를 사용한 경우가 가장 우수한 용해도를 보였다. 또한 PLH와 carrier의 비율이 1:2이상에서는 더 이상 용해도가 높아지지 않아 1:2로 최적화하였다. 흥미롭게도 다양한 medium에서 SD와 PM이 비슷한 용해도를 보였다. 알킬화제로 Na_2CO_3 를 첨가한 경우 탈이온화수에서는 급격한 용해도개선을 보였으나, PH 6.8에서는 효과가 없었다. Immediate Release Tablet으로 된 SD와 PM은 순수약물이나 Onon® 캡슐보다 더 높은 용출을 보였다. 순수약물, Onon® 캡슐의 Pranlukast가 30분만에 각각 3.4%, 1.9%의 용해도를 보인 반면에 SD와 PM은 각각 87.9%, 88.3%의 용해도를 보였다. 또한 SD와 PM으로 이루어

진 Tablet은 용해도 결과와 마찬가지로 비슷한 용출률을 보였다. FTIR결과에 따르면 PH 6.8완충용액의 성분인 Na^+ 는 Pranlukast와 산-염기 상호작용을 가지며, PLH 의 amide NH bond와 Kollidone® VA64의 carbonyl bond C=O사이의 수소결합이 존재하였다. Molecular simulation study에서도 PLH와 Kollidone® VA64 사이의 수소결합을 관찰할 수 있었다. 2D-NMR에 따르면, PM 제형에서 D2O에 Na_2CO_3 를 첨가한 경우 10.04 ppm에서 관찰되는 N-H 피크가 사라졌다. FTIR과 2D-NMR결과가 Pranlukast와 Kollidone® VA64사이에 강한 interaction이 존재함을 명시해주었다. 결과적으로 Pranlukast의 약산의 성질, Kollidone® VA64의 습윤효과, 알칼리 효과와 구성성분간의 interaction으로 인해 SD와 PM의 제형에 관계없이 용해도가 개선되었다. 그러나 제형 개발에서 SD보다 나은 간편성으로 인해 PM이 더 유리한 방법으로 여겨진다.

ABSTRACT

Strategies to improve solubility and dissolution of Pranlukast

By: Taksim Ahmed
Advisor: Prof. Hoo-Kyun, Choi, Ph.D.
Department of Pharmacy,
Graduate School of Chosun University

The purpose of the current study was to implement various formulation strategies to improve solubility and dissolution behavior of poorly soluble drug pranlukast. A solid dispersion (SD) system consisting of pranlukast and hydrophilic polymer Kollidon® VA64 at the weight ratio of 1:2 was prepared by solvent evaporation method. A simple physical mixture (PM) system with the same composition was prepared for comparative study. Differential scanning calorimetry and X-ray diffraction studies showed the presence of partial crystalline structure of pranlukast in SD formulation. Various hydrophilic polymers were screened as carrier for SD and PM formulations. Among all the carriers screened Kollidon® VA64 showed superior solubility in pH 6.8 buffer. And PLH to carrier ratio was optimized to 1:2 since no significant solubility enhancement was observed beyond 1:2. Interestingly, SD and PM showed similar solubility in various medium. Addition of alkalizer, Na_2CO_3, showed dramatic improvement of solubility in deionized water medium. However, alkalizer had no solubilization

effect in pH 6.8 buffer. Moreover, SD and PM based immediate release (IR) tablet showed greater dissolution profile than pure pranlukast or commercial Onon® capsule. About, 87.9 % and 88.3 % of the PLH was dissolved at 30 min in case of SD and PM tablet, respectively, whereas, only 3.4 % and 1.9 % of PLH was dissolved from pure drug and Onon® capsule, respectively. Moreover, SD and PM based tablet showed similar dissolution profile which coincided with the solubility results. From the FTIR study it was observed that buffer component of pH 6.8, Na+, can interplay an acid-base interaction with pranlukast during the solubilization procedure in buffer medium. Moreover, there was probable hydrogen bonding interaction between PLH amide NH bond and Kollidon® VA64 carbonyl bond (C=O). Molecular simulation study also revealed the formation of hydrogen bonding between PLH and Kollidon® VA64. 2D-NMR study revealed that the amide N-H peak at 10.04 ppm was disappeared upon addition of Na_2CO_3 in the PM system in D_2O medium. Along with FTIR and 2D-NMR study elucidated that there might be the presence of strong interaction between pranlukast, Kollidon® VA64. Concisely, weak acidic nature of pranlukast, wetting effect of Kollidon® VA64, alkalizing effect and interaction among the components might have led the enhance solubility of SD and PM formulation, regardless of the formulation type. Simplicity of PM over SD, however, makes it a lucrative delivery strategy for pranlukast formulation development.

1. INTRODUCTION

Poorly water soluble drug candidates are increasing due to the use of combinatorial chemistry and high-throughput screening tools during drug discovery (Lipinski et al., 2001). Approximately, 40 to as much as 70 % of all new chemical entities entering in the drug development programs are hampered owing to the insufficient aqueous solubility (David J, 2007), and more than 40% marketed drugs possess similar properties (Fahr and Liu, 2007). According to the biopharmaceutics classification system (BCS) or developability classification system (DCS), compounds having low solubility but high permeability are grouped as class II compounds; therefore, solubility enhancement is a part of the strategies to improve the oral bioavailability (Amidon et al., 1995; Butler and Dressman, 2010; Löbenberg and Amidon, 2000). Among the several approaches, solid dispersion (SD) has been demonstrated as a promising technique for improving the bioavailability of poorly water soluble drugs via the enhancement of their solubility and dissolution rate (Chiou and Riegelman, 1971; Leuner and Dressman, 2000). SD consists of a drug dispersed in a water-soluble carrier, using melting or solvent evaporation methods for preparation (Vasconcelos et al., 2007). However, commercialization of SD has been challenging due to the difficulty of optimizing and scaling-up of the preparation methods and stability problem during preparation and storage (Serajuddin, 1999). In addition, use of organic solvents in solvent

evaporation method raises the issues of toxicity, safety hazards and solvent residuals. In case of melting method, incomplete miscibility of drug and carrier may occur, and thermally unstable drugs can be degraded because of the relatively high processing temperature (Duncan Q.M, 2002; Leuner and Dressman, 2000).

Pranlukast, a selective anti-leukotriene drug, is widely used in the treatment of bronchial asthma (Keam et al., 2003). Pranlukast hemihydrate (PLH) (Fig. 1A) has solubility of 1.2 µg/mL in water at 25℃ (Ozeki et al., 2011). PLH is known to have log P and cLogP values of 4.71 and 5.065, respectively, and belongs to class II (TSRL, 2012). Furthermore, PLH is a weak acidic drug with the *pKa* value of approximately 5.0 (Chono et al., 2008). Various formulation approaches have been reported in the literature to overcome the limited solubility of PLH, including use of cyclodextrins, gelatin, spray-dried microparticles, α-glucosyl hesperidin (Hsp-G) and oral nanosuspension preparation (Chono et al., 2008; Mizoe et al., 2007; Niwa et al., 2011; Ozeki et al., 2011; Uchiyama et al., 2011; Wongmekiat et al., 2002, 2003). U.S. patent application 0077322 disclosed the SD formulation of pranlukast prepared by spray drying technique using hydroxypropyl methylcelluse (HPMC), hydroxypropyl cellulose and hydroxypropyl methylcellulose phthalate-50 (Lee, 2003). U.S. patent 5,876,760 reported the spray dried granules comprising of pranlukast, saccharides, surfactants and hydrophilic polymers (Sasatani, 1999). Furthermore, a preparation method for pranlukast SD

by hot-melt procedure including one or more water soluble polymer mainly Kollidon® VA64, polyvinyl pyrrolidone (PVP) and poly vinyl alcohol (PVA), was disclosed in WO 2006/049433 and WO 2007/024123 (Oh, 2006, 2007a).

In this study, a simple physical mixture of PLH and polymer (Kollidon® VA64) showed dramatic improvement in solubility. This finding paved the way to develop an efficient, convenient and cost-effective delivery system for PLH using physical mixture system instead of various sophisticated formulations available in the patents and articles. To the best of our knowledge, physical mixture based PLH formulation has not yet been reported.

2. MATERIALS AND METHODS

2.1 Materials

PLH was a gift from Yuhan Pharmaceuticals (Seoul, Korea). Polyvinylpyrrolidones (Kollidon® K-30 and Kollidon® K-90), vinylpyrrolidone-vinyl acetate copolymer (Kollidon® VA64), macrogol 15 hydroxystearate (Solutol® HS 15) were obtained from BASF (Ludwigshafen, Germany). Polyvinyl alcohol (PVA 89.000-90.000) was purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). Gelucire® 50/13 and Gelucire® 44/14 were obtained from Gattefossé (Lyon, France). Magnesium stearate, microcystalline cellulose (Avicel® PH-102) was a gift from BC World Pharm Co. Ltd. (Seoul, Korea). Croscarmellose sodium (VIVASOL®) was obtained from JRS Pharma (Rosenberg, Germany). Deuterated NMR solvents (DMSO-d6 and D_2O) were purchased from Cambridge Isotope Laboratories, Inc. (Andover, MA, USA). All other materials and reagents were of analytical grade and used as received without further purification.

2.2 Methods

2.2.1 Preparation of solid dispersion

Solid dispersion of PLH was prepared by solvent evaporation method. PLH and Kollidon® VA64 were weighted accurately and dissolved in dichloromethane:ethanol mixture (1:1). And the solvents were removed in vacuum dryer (NAPCO 5831, Fisher Scientific, MA, USA) for 12 hr. The dried samples were collected and triturated with mortar and pestle. The powder was passed through 50 mesh sieve.

2.2.2. Physical characterization of SD granules

2.2.2a Differential scanning calorimetry (DSC)

Thermal analysis was carried out using DSC unit (Pyris 6 DSC, Perkin Elmer, Netherlands). Indium was used to calibrate temperature scale and enthalpic response. Samples were placed in aluminum pans and heated at a scanning rate of 10 ℃/min from 50℃ to 290℃.

2.2.2b X-ray diffraction (XRD)

X-ray powder diffraction was obtained using X-ray diffractometer (X'Pert PRO MPD, PANalytical Co., Holland). The diffraction pattern was measured with a voltage of 40 kV and a current of 30 mA over a 2θ range of 2-50^{o} using a step size of 0.03^{o} at a scan speed of 1 s/step.

2.2.3 Fourier transform infrared (FTIR) spectroscopy

The spectra of the pure PLH, Kollidon® VA64, physical mixture, binary SD (PLH: Kollidon® VA64= 1:2), ternary SD with alkalizer (PLH:Kollidon® VA64: NaOH/KOH = 1:2:0.2) was determined by using an FTIR spectrophotometer (Spectrum 100, Perkin Elmer, USA). The wave length was set from 450-4000 cm^{-1}, and recorded with a resolution of 2 cm^{-1}. In addition, PLH, Kollidon® VA64, and PM were dissolved in pH 6.8 buffer, stirred for 24 hr and freeze dried by programmable freeze dryer (PVTFD 10R, Ilshin Lab., Korea). Freeze dried powders were subjected to FTIR studies as mentioned previously.

2.2.4 UV-Vis Spectroscopy

UV-Vis absorption spectra were recorded on a UV spectrophotometer (UV-

1601, Shimadzu, Japan). Pure PLH, Kolldion® VA64 and physical mixture system (PLH: Kollidon® VA64, 1:2) were dissolved in pH 6.8 buffer, and subjected to UV spectroscopy. The spectra were obtained in the λ = 800-200 nm range.

2.2.5 2D- Nuclear magnetic resonance (NMR) study

2D NMR study was conducted with the pure PLH, pure Kollidon® VA64 and physical mixture system. The samples containing 10 mg PLH were weighted in 2 mL eppendorf tube. D_2O (1mL) was used as a solvent for pure Kollidon® VA64 and PLH:Kollidon® VA64:Na_2CO_3 (1:5:0.2). DMSO-d6 (1 mL) was used as a solvent for pure PLH and PLH: Kollidon® VA64 (1:5) samples since they are not soluble in D_2O. After complete solubilization, samples were filtered through regenerated cellulose filter and subjected to NMR study. ^{1}H-NMR, ^{13}C NMR, HMBC and HSQC NMR spectra were recorded on a 600 MHz LC-Nuclear Magnetic Resonance Spectrometer-MS (Varian NMR system 600 MHz, Agilent Technologies, USA).

2.2.6 Solubility study

PM and SD prepared with various carriers at weight ratio of 1:5 was subjected to solubility test. PM and SD containing 5 mg PLH was added into 5 mL

and/or 10 mL of distilled water, pH 6.8 buffer (Fig. 2 and Fig. 4). Subsequently samples were stirred at 600 rpm with teflon coated magnetic bar for 24 hr at room temperature. Samples were then centrifuged at 13200 rpm for 10 min, filtered through 0.45 μm pore-sized regenerated cellulose syringe filter (Target®, National scientific, USA), suitably diluted with mobile phase, and analyzed by HPLC.

2.2.7 Tablet preparation with physical mixture system

Drug, polymer and other excipients were weighed accurately as per the composition mentioned in Table 1. Then the powders were mixed thoroughly and were sieved through 50 mesh sieve. Then oval shape tablet were prepared with rotary press (Chamunda Machinery Pvt. Ltd. Ahmedabad. India). The tablet hardness was maintained around 10.0-11.0 Kp.

2.2.8 *In vitro* dissolution studies

Dissolution studies of pure PLH powder, commercial products (Pranair® and Onon®), physical mixture, and solid dispersion tablets were performed using dissolution apparatus (DST-810 and DS-600A, Labfine Inc., Suwon, Korea) at 37 ± 0.5℃ and at the paddle speed of 100 rpm. The medium used for the study include 900 mL of pH 6.8 buffer. All the tested formulations contain 112.5 mg equivalent

amount of PLH. At predetermined time intervals, 2 mL of the samples were withdrawn and replaced with equal volume of fresh medium. The collected samples were filtered through regenerated cellulose syringe filter (Target®, National scientific, USA). Samples were then suitably diluted with mobile phase and analyzed by HPLC. Experiments were performed in triplicate and results expressed as mean percentage dissolved (±SD) at the given sampling time.

The difference and similarity factors between the formulations were determined using the data obtained from the drug release studies. The data were analyzed by the following equations (Moore, 1996).

Difference factor (f_1):

$$f_1 = \frac{\sum[R_t - T_t]}{\sum R_t} \times 100$$

For similarity factor (f_2):

$$f_2 = 50 \log\{[1 + 1/n \sum_{t=1}^{n} W_t (R_t - T_t)^2]^{-0.5} \times 100\}$$

where R_t and T_t are dissolution of reference and test products at time t, respectively, and f_1 is difference factor, f_2 is similarity factor, n is the number of time points. If f_1 is less than 15 and f_2 is greater than 50 it is considered that both products share similar drug release behaviors.

2.2.9 Statistical analysis

The statistical significance of the difference in the parameters was determined using the analysis of variance (ANOVA). A p-value < 0.05 was deemed to be statistically significant using a student t-test between the two means for the unpaired data. All data are expressed as mean ± standard deviation (SD).

2.2.10 HPLC analysis of pranlukast

The amount of PLH was determined using a high performance liquid chromatography (HPLC) system (Shimadzu Scientific Instrument, MD, USA), consisting of a UV detector (SPD- 10A), a pump (LC-10AD) and an automatic injector (SIL-10A). The mobile phase composition was acetonitrile / 20 mM KH_2PO_4 / methanol (5:5:1, v/v/v %) and the flow rate was 1.0 mL/min. The wavelength of the UV detector was 260 nm and a reversed-phase column (Luna 5µ C8 110A, Phenomenex, USA) was used.

3. RESULTS AND DISCUSSION

3.1 Characterization of solid dispersion by DSC and XRD studies

To improve the solubility and dissolution of PLH we implemented several formulation strategies in the current study. Solid dispersion (SD) is a widely used technique for enhancing the solubility and dissolution of poorly soluble drug via the structural changes of crystalline into amorphous form. In our study, SD of PLH was prepared by solvent evaporation method which improves its solubility and dissolution rate. Moreover, the physical mixture (PM) of PLH and various carriers, in which PLH and each carrier was simply mixed, was also prepared to compare with SD formulation. The solid state characteristics of SD were investigated using DSC and XRD to investigate the crystalline property of PLH in the formulations. The DSC thermograms of PLH and its SDs are shown in Fig. 2A. The degradation endothermic peaks of pure PLH crystal were observed at 193.71℃ and 200.45℃ (Ozeki et al., 2011), and melting peak was observed around 245.31℃. In case of PM, peaks around 190℃ were visible, however, no melting peak was observed. In case of SD, neither degradation peaks nor melting peak were observed, indicating that PLH crystallinity might be significantly reduced or drug existed in amorphous form. It was of interest to note that Kollidon® VA64 has glass transition temperature (T_g) of 104℃. At T_g, the amorphous polymer undergoes changes such as it softens,

and transition occurs from a glassy state to a rubbery state as a result of increased segmental molecular mobility (Nyamweya and Hoag, 2000). Thus, PLH might be melted/dissolved in the polymer as materials soften upon application of heat. Subsequently the melting peak of PLH was disappeared in case of PM formulation. However, the reason for appearance of the endothermic degradation peak in case of PM at around 190-200℃ is not clear (Ozeki et al., 2011).

XRD studies were performed to have greater insight into the crystallinity of PLH in SD formulation (Fig. 2B). It was observed that pure PLH had crystalline peaks at 3.32°, 9.92°, 14.53°, 16.63°, 19.96°, 20.56°, 23.52° and 26.87° position of 2θ. However, the major peaks of PLH at 14.53° and 16.63° were reduced and the characteristics peaks at 3.32°, 19.96°, 20.56° and 26.87° were disappeared in case of SD formulation (Fig. 2B, d). The result revealed that the PLH might present in partially crystalline form in SD formulation. On the other hand, Kollidon® VA64 exhibited no crystalline peak except an infinitesimal peak appeared at 5.64° (Fig. 2B, b). Surprisingly, a new peak appeared around 5.79° in case of SD formulation. It was reported that the x-ray diffraction pattern exhibiting the appearance of no new peak upon preparation of SD, therefore, absence of interaction between the drug and the carrier (Ahuja et al., 2007; Damian et al., 2000). However, in our study SD showed the appearance of new peak at 5.79°, which might be due to interaction between PLH and Kollidon® VA64. The potential interaction between

PLH and Kollidon® VA64 in SD formulation will be discussed further in the later section. In contrary, PM formulation showed similar diffraction spectrum with pure PLH having reduced peak intensity (Fig. 2B, c). Altogether, XRD and DSC analysis indicated that solid dispersion formation of PLH caused a change in the crystalline state of PLH to a partially amorphous.

3.2 Screening of carriers

In order to find the optimum carrier for PLH, solubility of PLH was measured using SD formulation prepared with various polymeric and non-polymeric carriers and compared with PM formulations. It was reported previously that the absorption site for PLH is upper part of the gastrointestinal tract (Uchiyama et al., 2011). So that, polymer screening studies was conducted in pH 6.8 buffer. As is clearly observed from Fig. 3, SD formulation containing Kollidon® VA64 was most effective in enhancing the solubility of PLH as compared to other polymers. PVP K90 and PVP K30 also showed better solubility but lower than Kollidon® VA64. Furthermore, Solutol® HS15, Poloxamer 407 or Poloxamer 188, Gelucire® 44/14 or Gelucire® 50/13 are surface active carriers, showed significantly lower solubility than Kollidon® VA64. To ascertain the solubility result, and to select the best polymer, dissolution study with the SD tablet composed of PLH:Kollidon® VA64, PLH:PVP K90 or PLH:PVP K30 at the weight ration of 1:2

were conducted in pH 6.8 buffer. Consequently, slower dissolution rate of PLH was observed in case of PVP K90 as well as PVP K30 (data not shown)so. Therefore, dissolution data was an indicative to select Kollidon® VA64 for further studies. It was interesting to note that regardless of the simple mixture of polymer and PLH in PM formulation, both SD and PM exerted similar solubility profile (Fig. 3). These results may indicate that major mechanism of solubilization is the presence of hydrophilic polymer which provided better wettability of the drug. Moreover, the wettability might have been influenced by drug polymer interaction. Thus, our later section would evaluate the probable interaction between drug and polymer in PM formulation, and elucidate the mechanism for similar solubility of PLH between PM and SD formulation.

Furthermore, solubility of the individual polymer in water was overlooked. And it was observed that solubility of individual polymer was as KollidonVA64> PVPK90> PVP K30> Solutol HS15> Poloxamer 407 > Poloxamer 188. Interestingly, the solubility of PLH along with various polymer showed linear relationship (r^2 = 0.91). In case of Gelucire 44/13, solubility was significantly low since it is dispersed in water. However, even though Gelucire 50/13 has very limited solubility in water, it showed enhanced solubility. Exact reason for this solubility improvement is not clear but it could be due to the surfactant effect on solubility enhancement. However, Eudragit S100 has good solubility in pH 7.0

buffer which would be the reason for better solubilization effect of this polymer.

In addition, the superiority of the Kollidon® VA64 among other hydrophilic polymers can be explained by various mechanisms. Several steps might be involved in the solubilization of PLH by Kollidon® VA64. Intrinsic solubilization capacity of the polymer is one of the important parameter which might be better in case of Kollidon® VA64 than other polymers. A recent study by Chono et al, 2008, showed that the dissolution property of the polymer itself was involved in solubilization of PLH. Wetting effect of the hydrophilic polymer is well known. Moreover, carbonyl groups in Kollidon® VA64 are capable of forming hydrogen bonds with acidic groups of drug (Albers et al., 2011). And there was an indication of probable interaction between PLH and Kollidon® VA64 in SD formulation which will be discussed in FTIR section. Thus, combining all the parameter including enhanced solubility of PLH in pH 6.8 buffer, Kollidon® VA64 was selected as the ultimate carrier for the SD and PM preparation of PLH in subsequent studies.

3.2.1 Effect of carrier ratio on solubility of PLH

In general, drug to carrier ratio affects the solubility of drug in aqueous medium. Moreover, reduction of final formulation, for instance, tablet size, and subsequent decrease in production cost is necessity. Thus, PLH to Kollidon® VA64

ratio was further optimized. For this purpose, PM system with varying proportion of PLH to Kollidon® VA64 was subjected to solubility test. As shown in Fig. 4, increasing the proportion of Kollidon® VA64 in the PM formulation increased the solubility of PLH significantly up to the weight ratio of PLH:Kollidon® VA64 at 1:2. As the drug to carrier ratio was increased further from 1:2 to 1:10, no significant enhancement in solubility was observed. Thus, PLH:Kollidon® VA64 at 1:2 was regarded as the optimum proportion for further studies.

In addition, the effect of polymer concentration on solubility of PLH in unit volume of pH 6.8 buffer was investigated. The solubility of PLH was assessed by adding various amounts of PM in the same volume of medium. Adding more PM in a fixed volume of medium would result in higher concentration of polymer. As can be seen from Fig. 5, the concentration of polymer in medium had a profound effect on the solubility of PLH. As the polymer concentration increases in unit volume of medium, solubility of PLH enhanced linearly (r^2= 0.9964). Similar types of results had been reported exhibiting linear regression between drug solubility and polymer concentration (Nepal et al., 2010; Sethia and Squillante, 2004). Solubility enhancement of PLH seems to be the solubilization effect of the polymer. Hence, the total percentage of dissolved PLH remained nearly constant irrespective of the amount of the PM formulation taken.

3.3 Comparative solubility of PLH between SD and PM formulations

As can be seen from Table 2, the pure PLH has solubility of 1.72 µg/mL in deionized water. Moreover, the solubility was determined in various pH buffers. The solubility of PLH in pH 1.2, 3, 5, 6.8, 7.4 and 10 buffers was 0.50, 1.89, 5.72, 8.31, 8.25 and 8.10 µg/mL, respectively. Thus, the solubility of PLH was dependent on pH, being highly soluble in basic conditions but relatively insoluble in deionized water and acidic pH condition. However, in case of SD formulation (PLH:Kollidon® VA64, 1:5) solubility was significantly improved in pH 6.8 buffer around 1 mg/mL as compared to water, around 45.0 µg/mL (Table. 2). As the PLH to Kollidon® VA64 ratio was reduced to 1:2, the solubility was not affected significantly. At PLH:Kollidon® VA64 (1:2), the solubility of PLH in 6.8 buffer was 946.80 µg/mL. Nonetheless, SD formulation was prepared with solvent evaporation method using dichloromethane and ethanol. Thus, an alternative formulation strategy is required which could bypass the overwhelming problems of SD formulation. In this context, while comparing the SD with the PM formulations, surprisingly similar solubility results were observed. As can be seen from Table 2, the solubility of PLH in PM formulation (PLH:Kollidon® VA64, 1:5) also significantly improved in pH 6.8 buffer (around 980.46 µg/mL). Moreover, the solubility of PLH in PM (PLH:Kollidon® VA64, 1:2) formulation was 923.77 and 0.56 µg/mL in 6.8 buffer and 1.2 buffer, respectively. These results render an

opportunity to develop an efficient and lucrative delivery system for PLH using PM instead of sophisticated SD formulation system.

To investigate the active role of pH 6.8 buffer in solubility enhancement of PLH, we have investigated the effect of buffer concentration (ranging from 50 to 1 mM) on solubility of PM formulation. As illustrated in Fig. 6, the higher the buffer concentration, faster the PLH flux. In addition, buffer concentration up to 15 mM, solubility of PLH was maximum, around 500 µg/mL, followed by gradual decrement in solubility. This signifies that phosphate buffer concentration of 15 mM was sufficient to solubilize PLH at 1 mg/mL concentration level. Calculated amount of buffer component NaOH present in 15 mM buffer concentration was about 0.3 mg/mL. Subsequently, solubility study of PM formulation was conducted in deionized water along with NaOH and NaH_2PO_4. Among the buffer component, NaOH was found to be the key effecter on solubility enhancement of PLH than NaH_2PO_4 (data not shown). Precisely, this study revealed the role of alkalizer in solubility enhancement of PLH in deionized water medium. Moreover, several reports has been published that incorporation of pH modulator can improve the solubility and dissolution behavior of poorly soluble ionizable drugs (Tran et al., 2010). Thus, we have carried out solubility study of PLH using different alkalizer (0.02 w/v%) in water. As can be seen from Table 3, solubility of PLH was increased significantly comparing with the PLH powder (1.72 µg/mL, Table 2)

after addition of alkalizer except for MgO, $Mg(OH)_2$, $Ca(OH)_2$, $CaHPO_4$, $Al(OH)_3$. Among the alkalizers screened, NaOH showed the highest solubility enhancement followed by KOH and Na_2CO_3. However, Na_2CO_3 was chosen for further studies due to the hygroscopic nature and toxicity concern of NaOH and KOH. In addition, it is observed form the medium pH at 24 hr that upon addition of alkalizer in water (Table 3), pH was increased significantly. However, no correlation was observed between the pH of the solution and solubility (r^2= 0.0072) or *pKa* value of the alkalizer and solubility (r^2= 0.4527).

As the alkalizer showed profound solubilization effect, we have investigated the additional effect of incorporating alkalizer in our SD formulation to improve solubility of PLH in water. As can be seen form Table. 2, incorporation of Na_2CO_3 in SD system, showed significant improvement in solubility of PLH in water, around 996.45 µg/mL which is significantly higher for the formulation without Na_2CO_3 (45.0 µg/mL). Similar results were observed in case of PM formulation. Upon addition of alkalizer with SD and PM formulation, medium pH was increased from 5.80 to around 8.0. Thus, ionization of weak acidic PLH might have occurred which in turn provided significantly improved solubility in deionized water. The mechanism for this enhanced solubility upon addition of alkalizer will be discussed in more details in FTIR section. However, as is observed form Table 2, solubility of SD in pH 6.8 buffer without Na_2CO_3 and with Na_2CO_3

was 946.0 µg/mL and 936.67 µg/mL, respectively. This result indicates that SD formulation with alkalizer (Na_2CO_3) had no effect in solubilization of PLH in pH 6.8 buffer. The phenomenon was similar in case of PM formulation. This could be owing to the higher buffering capacity of pH 6.8 buffer, Na_2CO_3's inability to alter the buffer pH, possesses small molecular mass and high solubility in buffer media.

Concisely, alkalizer provided combined solubilization effect while incorporated in SD and PM formulations in water medium, and an efficient system to improve solubility and dissolution of PLH along with SD and PM formulation in water medium.

3.4 Fourier transform infrared spectroscopy (FTIR) study

FTIR study was carried out to elucidate the interaction between drug and polymer, and underlying mechanism involved in solubilization by alkalizer. FTIR spectrum of pure PLH (Fig. 1A) is observed form the Fig. 7A (a). PLH tetrazole N-H band was observed around 3429.50 cm^{-1}, secondary amide stretching band at 3301.10 cm^{-1}, secondary amide carbonyl band stretching at 1662.29 cm^{-1}, 1645.71 cm^{-1} and C-H band at 2941.38 cm^{-1}. As can be seen from Fig. 7A (b), Kollidon® VA64 (Fig. 1B) showed the characteristics amide peak at 3471.33 cm^{-1}, amide carbonyl (C=O) peak at 1677.31 cm^{-1}, acetate carbonyl peak (C=O) at

1740.82 cm^{-1}. However, as expected no interaction was observed in case of physical mixture system (PLH:Kollidon® VA64, 1:2) between the drug and polymer (Fig. 7A c). Noteworthy, in case of SD (PLH:Kollidon® VA64, 1:2) formulation tetrazole peak of PLH shifted from 3429.50 cm^{-1} to 3443.96 cm^{-1} (Fig 7A d). Moreover, the acetate carbonyl peak of Kollidon® VA64 was shifted slightly from 1740.82 cm^{-1} to 1736.64 cm^{-1}. In addition, drug carbonyl and the Kollidon® VA64 carbonyl merged together and showed a single peak at 1661.62 cm^{-1}. This signifies that Kollidon® VA64 undergoes interactions with PLH. Thus, shifting of the peak might be due to the formation of hydrogen bond between drug tetrazole hydrogen and Kollidon® VA64 carbonyl oxygen. This could be the reason for appearance of an extra peak in XRD study of SD samples (Fig. 2B d). However, to elucidate the role of buffer component (NaOH) in pH 6.8 buffer for solubility enhancement of PLH, we have incorporated NaOH in SD formulation which showed the strong interaction with tetrazole N-H group of PLH. Tetrazole N-H peak was disappeared (deprotonation) owing to the Na+ (Fig. 7A (e)). In addition, secondary amide peak intensity was significantly reduced at 3301.10 cm^{-1}. Previous findings showed the lewis acid-base interaction between the alkalizer and weakly acidic drug telmisartan and aceclofenac, and subsequent enhancement in solubility as well as *in vitro* dissolution rate (Tran et al., 2008; Tran et al., 2009). As is observed form Table 2, SD and PM with alkalizer (Na_2CO_3), exhibits enhanced solubility in water. This would be the attributes of presence of alkalizer effect inside the system.

However, solution state (drug, polymer and alkalizer solution in pH 6.8 buffer) FTIR would provide better insight of the underlying solubilization mechanism of PLH in aqueous medium. But, it was not possible to measure the liquid state FTIR due to the strong interference of H_2O molecule in the spectra. Hence, FTIR study was conducted with the physical mixture system (PLH:Kollidon® VA64, 1:2) stirred in pH 6.8 buffer, filtered through regenerated cellulose filter, afterward, freeze dried (Fig. 7B). Pure drug and polymer spectrum are shown in Fig 7B (a) and Fig. 7B (b), respectively. As can be seen from Fig. 7B (c), PM system showed reduced intensity of the characteristic peaks of PLH. Surprisingly, amide N-H peak of the drug at 3301.10 cm^{-1} disappeared and shifted tiny peak appears at 3362.06 cm^{-1}. This shifted peak might be owing to the formation of hydrogen bonding between N-H functional group of PLH and amide carbonyl (C=O) group of Kollidon® VA64. E. Karavas et al showed the formation of hydrogen bonding between NH group of felodipine and PVP carbonyl group (Karavas et al., 2007; Karavas et al., 2006). In addition, tetrazole NH peak at 3429.5 cm^{-1} was also disappeared. Acid-base interaction of drug and alkalizer might be the reason for this change. Moreover, there was shift of the carbonyl group of Kollidon® VA64 from 1740.82 cm^{-1} to 1735.48 cm^{-1}, and merge between the carbonyl peak of PLH at 1662.29 cm^{-1}, 1645.71 cm^{-1} and Kollidon® VA64 at 1677.31 cm^{-1}. The merged peak appeared at 1665.04 cm^{-1}. This might be the indication of involvement of polymer as interactive part with drug. In addition, PLH:Kollidon® VA64 at 1:5 also showed the

similar result (data not shown).

3.5 2D-NMR study of physical mixture system in solution state

NMR is a powerful tool for the identification of drug molecules and quantitative applications valuable to pharmaceutical analysis. Thus, 2D-NMR study of PM system was conducted to observe the interaction of drug and polymer in the solution state. Hence, in 2D-NMR study, HMBC and HSQC analysis confirmed the exact chemical shift of proton and carbon, and are depicted in Fig. 1A and B for PLH and Kollidon® VA64, respectively. As can be seen from Fig. 8(A), due to the strong resonance of the tetrazole group, the proton was not detected in pure PLH. However, amide NH proton was confirmed at 10.04 ppm. In case of Kollidon® VA64 (Fig. 8(D)), showed broad type of peak due to the presence of excessive amount of proton and carbon (Taghizadeh and Foroutan, 2004). All characteristics peaks of drug and polymer were present with the formulation PLH:Kollidon® VA64 (1:5) dissolved in DMSO-d6 (Fig. 8C). This indicated that there might be no strong interaction between the drug and polymer alone dissolved in DMSO-d6. However, from Fig. 8(B), it is observed that the PM (PLH: Kollidon® VA64:Na_2CO_3, 1:5:0.2) in D_2O, reflects the disappearance of the amide N-H peak at 10.04 ppm. This might be the indication of the strong interaction among drug, polymer and alkalizer (Na_2CO_3) in aqueous medium (D_2O). Assuming

that PLH and Kollidon® VA64 undergoes a hydrogen bonding interaction; 2D-NMR study might have shown the amide N-H peak. However, disappearance of the peak could be due to the shift of NH bond upon interaction, and shifted proton peak might have overlapped with other protons since polymer contains a large number of protons in the formulation. Interestingly, the ^{13}C position of PLH in 2D-NMR study showed that the surrounding environment of the N-H stretching bond was affected. It was found that the carbonyl peak at 165.23 ppm was shifted to 166.09 ppm and N-C peak at 148.45 ppm to 149.25 ppm (Fig. 1A). This chemical shift of carbon position further supports the interaction in N-H bond. However, along with the FTIR data as illustrated in Fig. 7B(c) and 2D-NMR data (which shows the disappearance of the amide NH group from 10.04 ppm), we can conclude that there might be the presence of strong interaction, which in turn provided better wettability, and responsible for good solubility and dissolution rate of PLH in aqueous medium. Thus the FTIR study was well correlated with the NMR study.

3.6 Molecular simulation studies

In order to confirm the drug polymer interactions, molecular simulation study was conducted to theoretically evaluate the possibility of our experimental results. Thus, the molecular simulation study of Kollidon® VA64 and PLH revealed the strong possibility of hydrogen bond formation, and the Kollidon® VA64 orientation

facilitates the compact fit of PLH in the polymer chain (Fig. 9 A and B). The polymer carbonyl group and the drug amide NH group showed a bonding with the bond length of 2.5 Å, which is the indication of hydrogen bond. Moreover, the binding energy 4.63 resembles the tight interaction and Van Der waals force of -7.4 revealed the strong hydrophobic interaction. Thus, polymer might be close enough to provide better wettability to the drug due to the compact fit of PLH in Kollidon® VA64 chain. Thus, simulation study also supports the drug polymer interaction which might be the probable reason for enhanced solubility in PM as well as in SD system.

In order to explain the interaction at a specific drug to polymer ratio, we have calculated the molar ratios between PLH and Kollidon® VA64 repeat unit in the formulation. The molecular weight of PLH and Kollidon® VA64 repeat unit is 490.51 and 197.2, respectively. Thus, the sizes of the Kollidon® VA64 repeat unit is much smaller than that of the molecule of PLH. Therefore, at the weight ratio of PLH: Kollidon® VA64, 1:2, molar ratio was calculated 1:4.97. Consequently, the amount of Kollidon® VA64 at this ratio might be adequate to interact with the whole amount of PLH, resulting in a hydrogen bonding and consequently increased the solubility of PLH.

3.7 *In vitro* dissolution study

Tablets containing SD and PM were prepared after adding various excipients to optimize dissolution characteristics (Table. 1) and dissolution study was conducted with different formulations. As illustrated in Fig. 10, the SD tablet as well as the PM based tablet showed similar dissolution profile which coincided with the solubility results. Furthermore, SD and PM tablets were able to exert significantly higher dissolution rate with respect to pure PLH and commercial Onon® capsule. About, 87.9 % and 88.3 % of the PLH was dissolved at 30 min in case of SD and PM tablet, respectively. In contrary, only 3.4 % and 1.9 % of PLH was dissolved from pure PLH and Onon® capsule, respectively. Since, SD contained the drug partially crystalline; consequently the drug release was mainly influenced by the carrier.

There might be several mechanism interplays simultaneously during the dissolution process of PLH in pH 6.8 buffer. First, drug solubility depends on the concentration of the polymer present in the medium (Fig. 5). From the Noyes-Whitney equation it can be concluded that the drug solubilization depends on the wetting of the surface of the drug crystal in medium. Thus the surface tension of the medium reduces and polymer provides better wettability. Moreover, hydrogen bonding interaction between drug and Kollidon® VA64 might have aided the

wetting effect of Kollidon® VA64. A boundary layer generates in which wetted drug particles are surrounded by the polymer prior to release in the medium. Furthermore, while exposing the PLH formulations to the buffer media there are probable possibilities of poor water penetration and also subsequent recrystallization or agglomeration of PLH during its contact with aqueous media. However, one of the additional properties of Kollidon® VA64 is its ability to inhibit drug recrystallization (Bley et al., 2010). Therefore, the probable precipitation chance in the buffer media during the dissolution was inhibited. This provides the smaller size drug particles surrounded by polymer layer in the medium. The drug's intrinsic structure is now exposed to the buffer component of the pH 6.8 buffer medium. As we know the buffer components consists of NaOH, NaH_2PO_4 and H_2O. Initially, there are possibilities to break the hydrogen bonding between the polymer and drug as there are H_2O molecules in the medium. $–OH^-$ will interfere with the NH group of the drug and lessen the drug polymer interaction (Tantishaiyakul et al., 1999). Secondly, acid-base interaction will take place in the medium, since the PLH is a weak acidic drug (pKa=5). As per sheng et al., 2009, at the solid surface of the drug molecule and the buffer component, several equilibrium reactions might take place. Thus, drug becomes ionized rapidly and there might be the formation of soluble Na-salt. Korean patent No. 10-2007-0055430 disclosed the medically usable salt of PLH (Oh, 2007b). Thus, ionized form and soluble salt form together increases the solubility as well as the dissolution of PLH regardless

of the physical states of the PLH e.g. partially amorphous structure as shown in XRD in case of SD formulation (Fig. 2B d). In addition, E. Karavas et at, 2006 showed that presence of interaction between drug and polymer facilitated the drug release. They also showed that the solubility and dissolution of drug from the solid dispersion formulation was influenced by the interactions took place in the solution between drug molecules and the macromolecular chains of the polymer (Karavas et al., 2007). Nonetheless, similar dissolution results between SD and PM formulation resembles the superiority of PM formulation over SD formulation. Concisely, the dissolution might be enhanced not only by the improved wettability of PLH in presence of Kollidon® VA64 but also by buffer component inter-played an acid-base interaction. Thus, combined effect drove the system to dissolve PLH rapidly.

Since alkalizer was responsible for the improved dissolution rate of PLH in pH 6.8 buffer. Our further study with PM formulation in water medium was conducted. From Fig. 11 it is observed that the drug dissolution rate in water was significantly improved while addition of alkalizer along with the Kollidon® VA64. Whereas, PLH:Na_2CO_3 showed 65.18 % dissolution of PLH at 1 hr and remained steady up to 12 hr. PLH:Kollidon® VA64 (1:2) and pure PLH showed significantly lower dissolution rate, 5.8 % and 1.72 %, respectively, comparing with other two formulation at 1 hr. This signifies the slight improvement of PLH dissolution upon addition of Kollidon® VA64. However, in case of PM formulation (PLH:

Kollidon® VA64: Na_2CO_3, 1:2:0.2), at 1 hr about 76.5 % and at 12 hr about 89.72 % drug was dissolved. Overall, the data reflects that the dissolution was influenced by the alkalizer, Na_2CO_3 as well as Kollidon® VA64. These results coincided with the solubility data of SD and PM formulations along with alkalizer Na_2CO_3 in water (Table 2). Furthermore, 2D-NMR study showed interaction between the drug, polymer and alkalizer, is an indicative of the enhanced solubility. Thus, the hydrophilic polymer rendered as wetting enhancement and the Na^+ from the alkalizer acted as acid base interaction mediator and aided in PLH ionization. Consequently dissolution rate was enhanced.

3.8 Statistical analysis for similarity and difference factor

The similarity factor has been adopted by the Center for Drug Evaluation and Research (FDA) and Human Medicines Evaluation Unit of The European Agency for the Evaluation of Medicinal Products (EMEA) as a criterion for the assessment of the similarity between two *in vitro* dissolution rates (CDER, 1995; EMEA, 1999). FDA and EMEA suggest that two dissolution profiles are declared similar if f_1 values lower than 15 (0–15) and f_2 is between 50 and 100. In the current study the commercial Pranair® capsule (SK Chemical Co. Ltd., Korea) which was prepared by hot-melt method, was taken as a reference drug (Oh, 2006, 2007a). And dissolution was compared with our SD and PM based immediate release (IR)

tablets at the time point of 0.5, 0.45, 1 and 2 hr. The similarity factor (f_2) for SD and PM formulation was found 61.27 and 61.89, respectively. And the difference factor (f_1) was obtained 5.78 and 5.27 for SD and PM tablet, respectively. The results indicates that SD and PM based IR tablet is capable to exert the similar dissolution profile of Pranair® capsule. In turn, this would be the indication for *in vitro* bioequivalence of PM and SD formulation with commercial product. In addition to this, PLH, being BCS class II compound, an increase in solubility would increase the bioavailability (Amidon et al., 1995).

4. CONCLUSIONS

Present study has demonstrated that SD and PM formulation showed significant improvement in solubility of PLH. Optimized tablet formulation of SD and PM exhibited stark difference in dissolution as compared to the commercial tablet. No organic solvents or sophisticated manufacturing process were required for PM formulation. Thus physical mixture formulation was superior to solid dispersion formulation on the basis of ease of preparation. Current finding paved the way to design a comprehensive preparation method for pranlukast dosage form development. Since pranlukast is BCS class II drug, the developed dosage form could be beneficial in improving bioavailability. However, *in vivo* studies should be performed to have better insight of the results obtained in the present study.

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Table 1.

Composition for immediate release tablet

PLH	Kollidon VA64	Na_2CO_3	Avicel PH 102	Mg stearate
112.5	225	22.5	135	5

Table 2.

Comparative solubility study with PM and SD system (mean ± SD, n = 3).

Media	Solubility (µg/mL)
PLH in water	1.72 ± 0.40
PLH in pH 1.2 buffer	0.50 ± 0.31
PLH in pH 3.0 buffer	1.89 ± 0.49
PLH in pH 5.0 buffer	5.72 ± 1.28
PLH in pH 6.8 buffer	8.31 ± 1.60
PLH in pH 7.4 buffer	8.25 ± 1.19
PLH in pH 10 buffer	8.10 ± 0.83
Solubility in pH 6.8 buffer	
PM, PLH:Kollidon® VA64, 1:5	980.46 ± 13.16
SD, PLH:Kollidon® VA64, 1:5	1004.25 ± 10.56
PM, PLH:Kollidon® VA64, 1:2	923.77 ± 12.86
PM, PLH:Kollidon® VA64:Na_2CO_3, 1:2:0.2	904.44 ± 18.35
SD, PLH:Kollidon® VA64, 1:2	946.80 ± 7.49
SD, PLH:Kollidon® VA64:Na_2CO_3, 1:2:0.2	936.67 ± 36.07
Solubility in deionized water	
SD, PLH: Kollidon® VA64, 1:5	45.00 ± 0.34
PM, PLH:Kollidon® VA64, 1:5	20.97 ± 0.2
SD, PLH: Kollidon® VA64:Na_2CO_3, 1:2:0.2	996.45 ± 10.30
PM, PLH:Kollidon® VA64:Na_2CO_3, 1:2:0.2	988.47 ± 9.79
Solubility in pH 1.2 buffer	
PM, PLH:Kollidon® VA64, 1:2	0.56 ± 0.14

Table 3.

Solubility of PLH in 0.02% w/v alkalizer solution (mean ± SD, n = 3).

Media	Solubility of PLH in media (μg/mL)	pH of solution at 24h
0.02% alkalizer in deionized water		
NaOH	78.99 ± 4.19	10.52
Na_2CO_3	44.39 ± 5.97	7.76
$NaHCO_3$	25.28 ± 5.98	7.25
$Na_2B_40_7.10H_2O$	22.97 ± 1.85	7.06
Na_2HPO_4	16.90 ± 2.76	6.69
KOH	68.59 ±14.47	7.52
$KHCO_3$	19.56 ± 3.77	7.12
K_2HPO_4	25.72 ± 7.67	6.76
$(NH4)_2CO_3$	24.36 ± 5.11	7.14
MgO	2.75 ± 0.15	9.85
$Mg(OH)_2$	1.30 ± 0.21	9.23
$CaCO_3$	6.39 ± 3.56	7.52
$Ca(OH)_2$	3.05 ± 0.18	10.55
$CaHPO_4$	0.92 ± 0.32	6.50
$Al(OH)_3$	0.76 ± 0.28	8.22

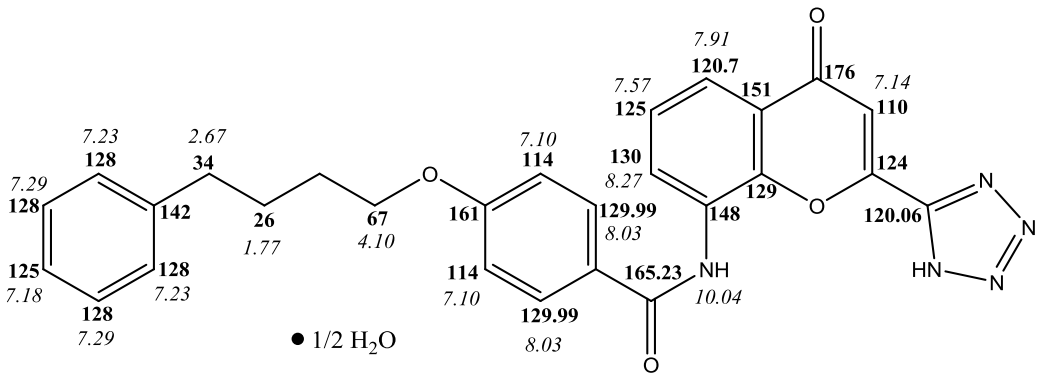


Figure 1(A). Pranlukast, Italic numerical indicates proton and bold numerical indicates the carbon chemical shift.

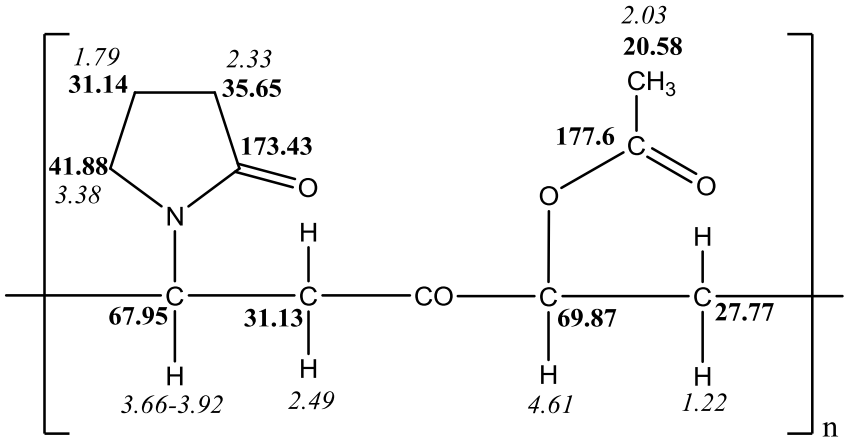


Figure 1(B). Kollidon® VA64, Italic numerical indicates proton and bold numerical indicates the carbon chemical shift.

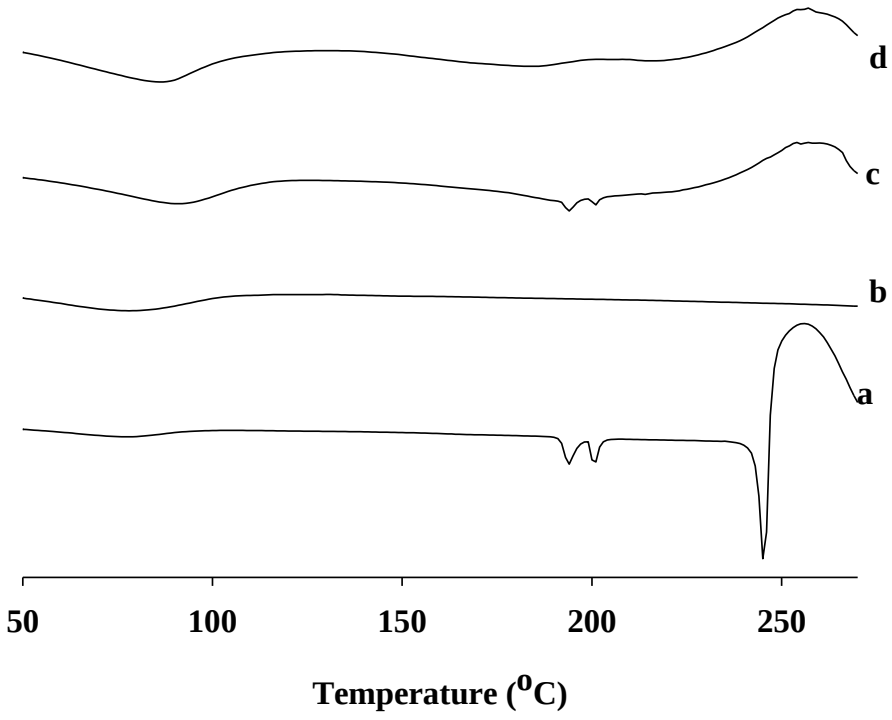


Figure 2(A). DSC thermograms (a) pure PLH, (b) Kollidon® VA64, (c) PM (PLH: Kollidon® VA64 = 1:2), (d) SD (PLH: Kollidon® VA64 = 1:2).

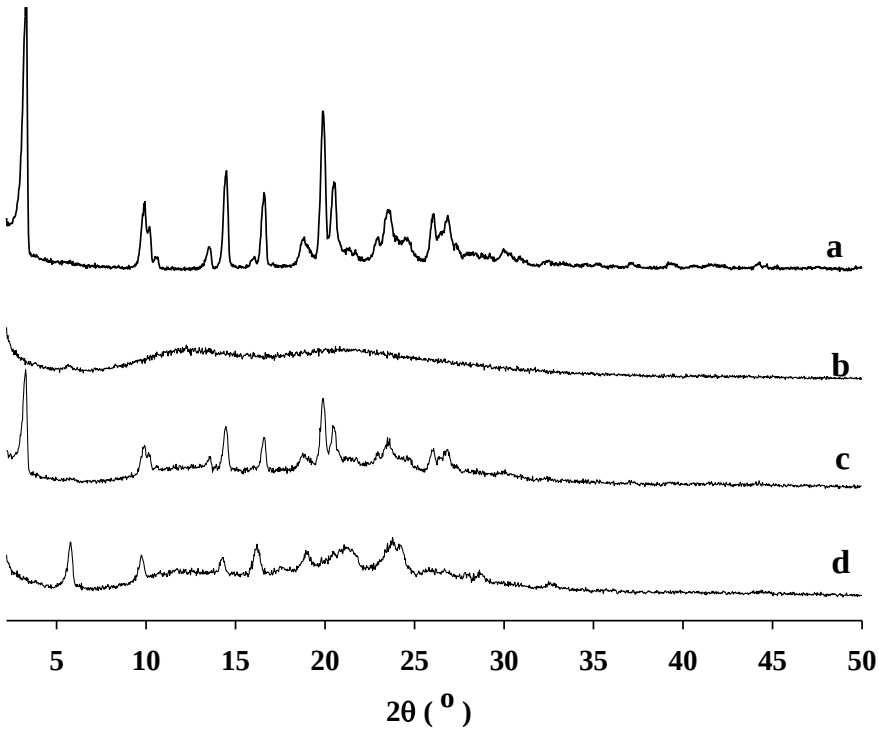


Figure 2(B). XRD patterns. (a) pure PLH, (b) Kollidon® VA64, (c) PM (PLH: Kollidon® VA64 = 1:2), (d) SD (PLH: Kollidon® VA64 = 1:2).

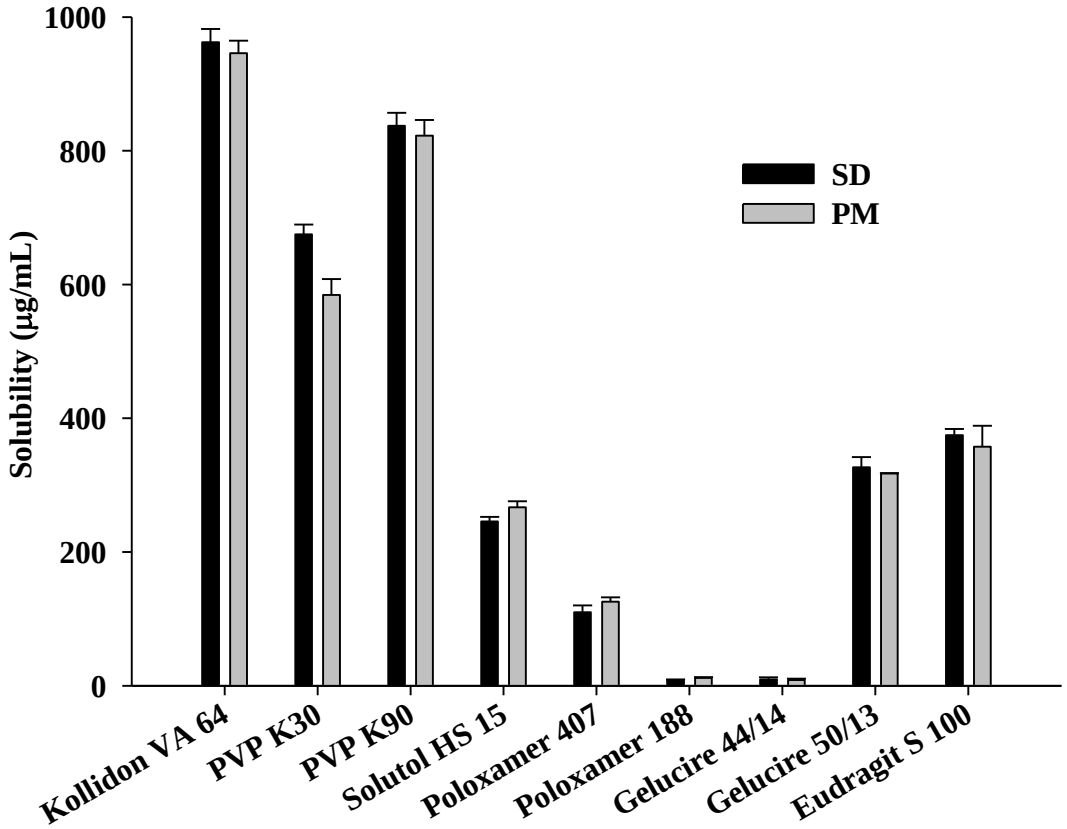


Figure 3. Polymer screening in pH 6.8 buffer (mean ± SD, n = 3).

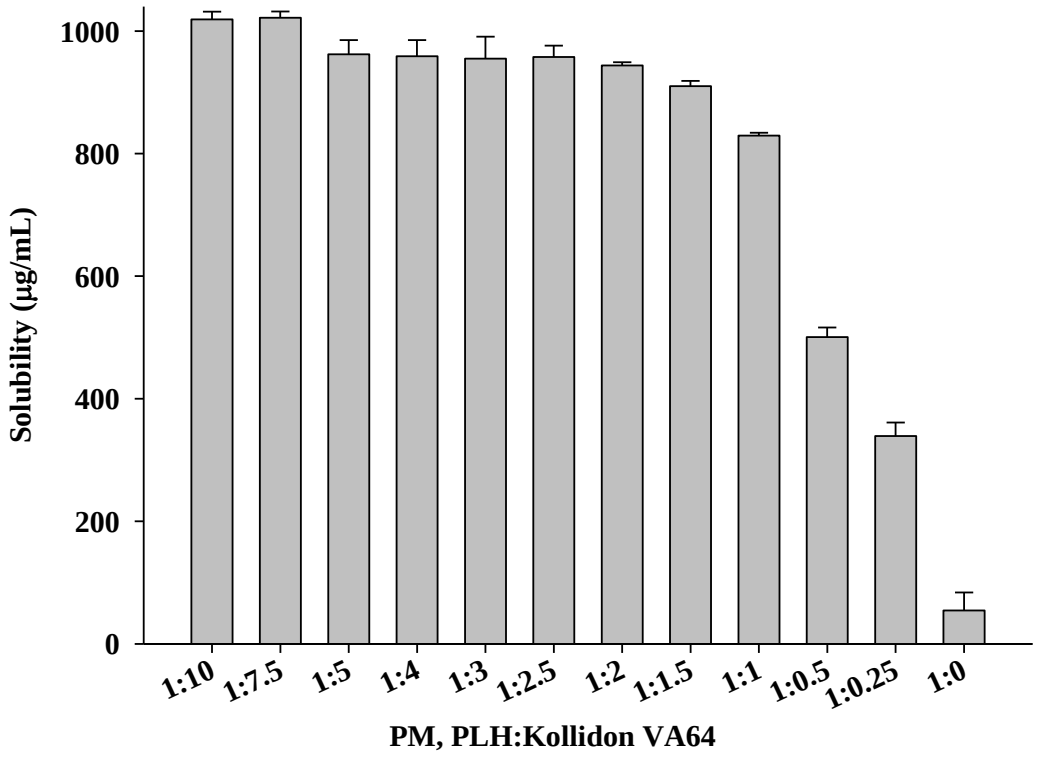


Figure 4. Solubility of PLH at various drug to polymer ratio in deionized water along with PM:Na_2CO_3= 1: 0.2 (mean ± SD, n = 3).

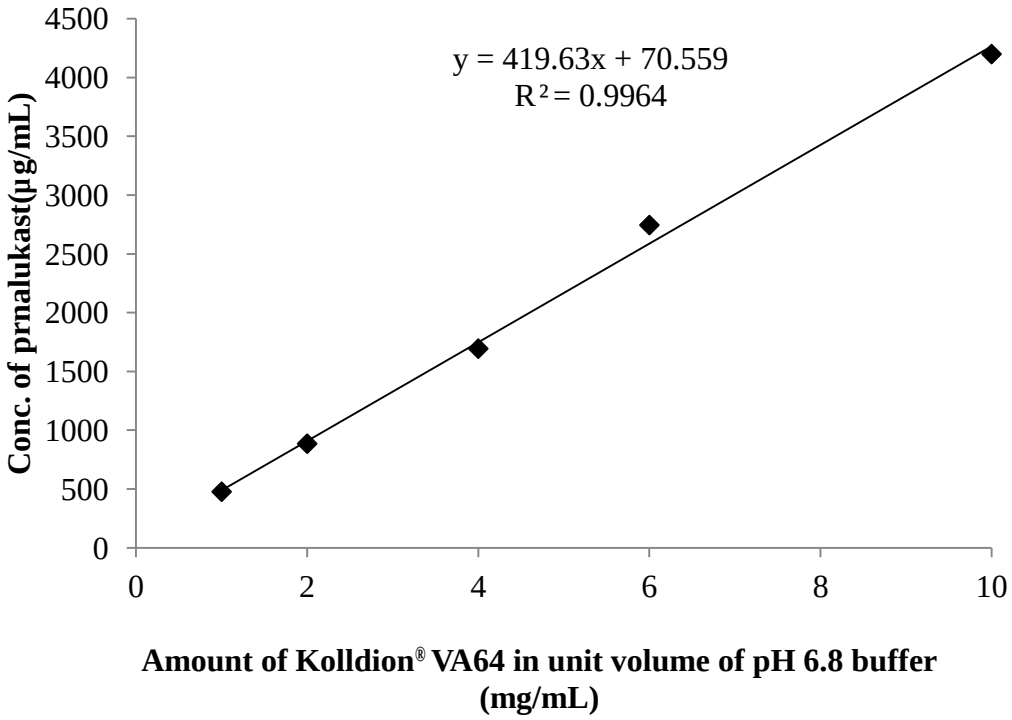


Figure 5. Effect of polymer concentration in medium on the solubility of PLH (mean ± SD, n = 3).

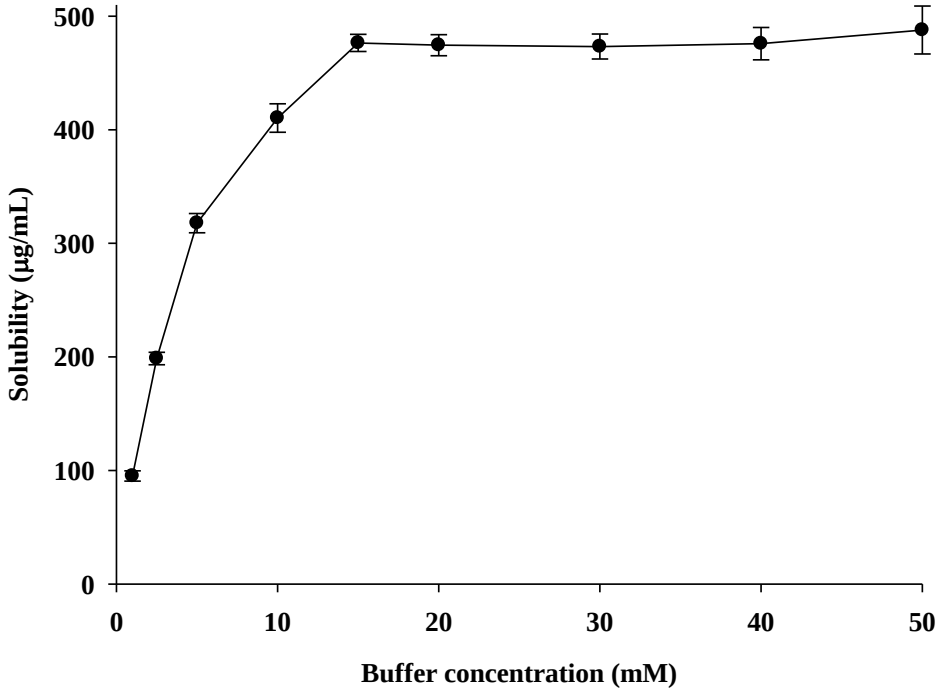


Figure 6. Solubility of PLH physical mixture system (PLH: Kollidon® VA64, 1:5) as a function of pH 6.8 buffer concentration (mean ± SD, n = 3).

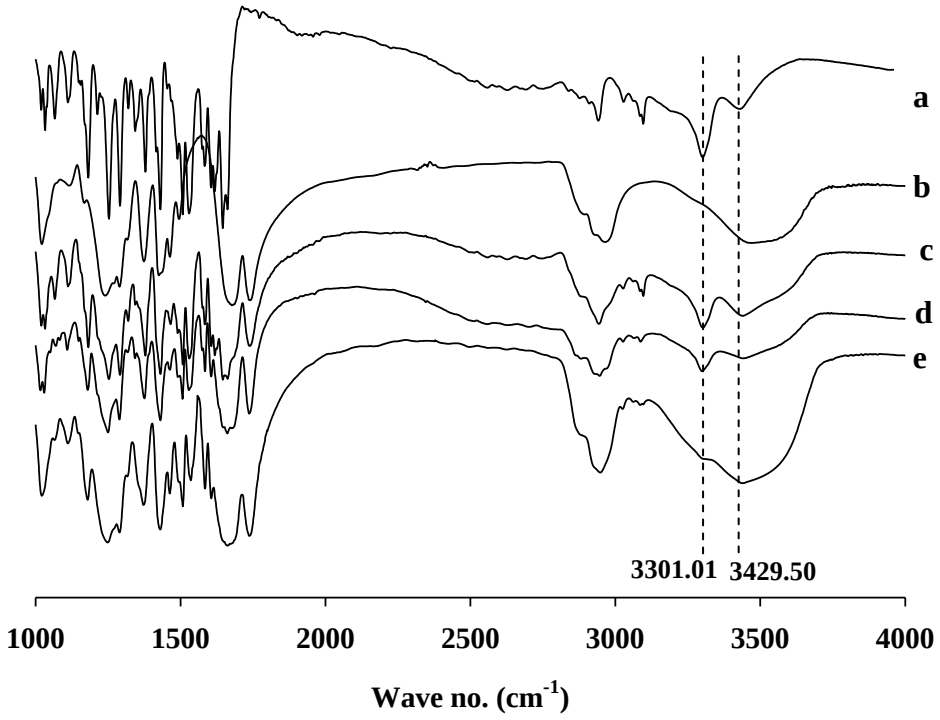


Figure 7(A). FTIR study of a) pure PLH; b. Kollidon® VA64, c. PM; d. SD; e. SD with NaOH.

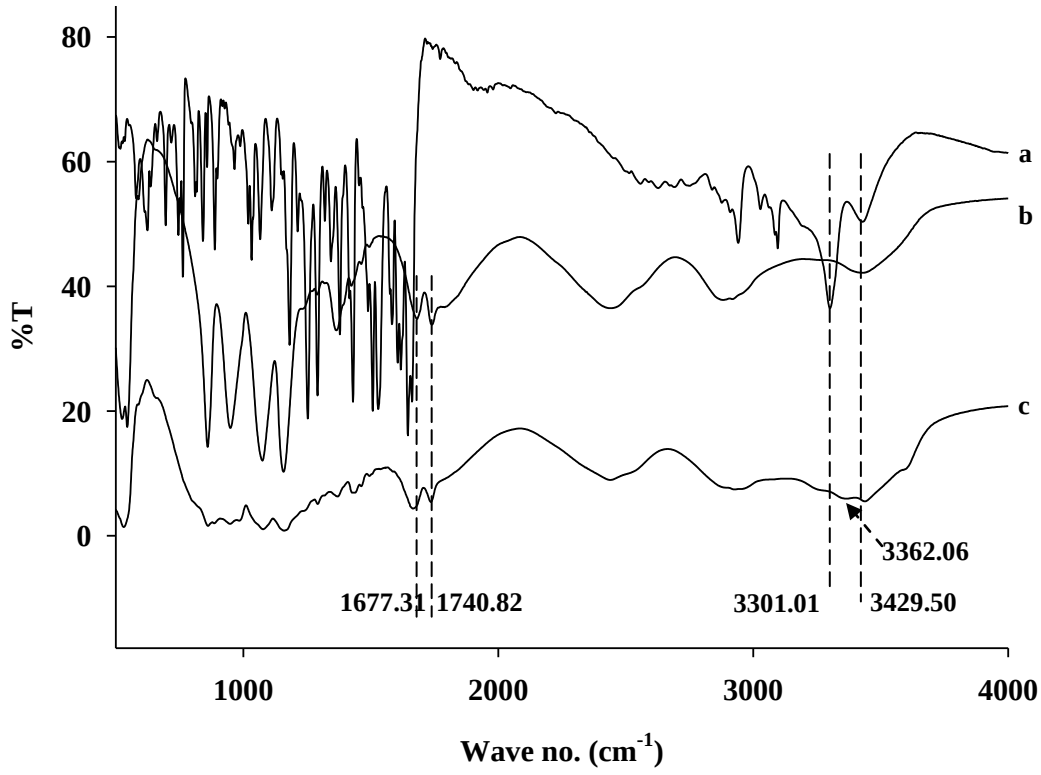


Figure 7(B). FTIR study of lyophilized samples. a. pure PLH; b. Kollidon® VA64 and c. PM in pH 6.8 buffer.

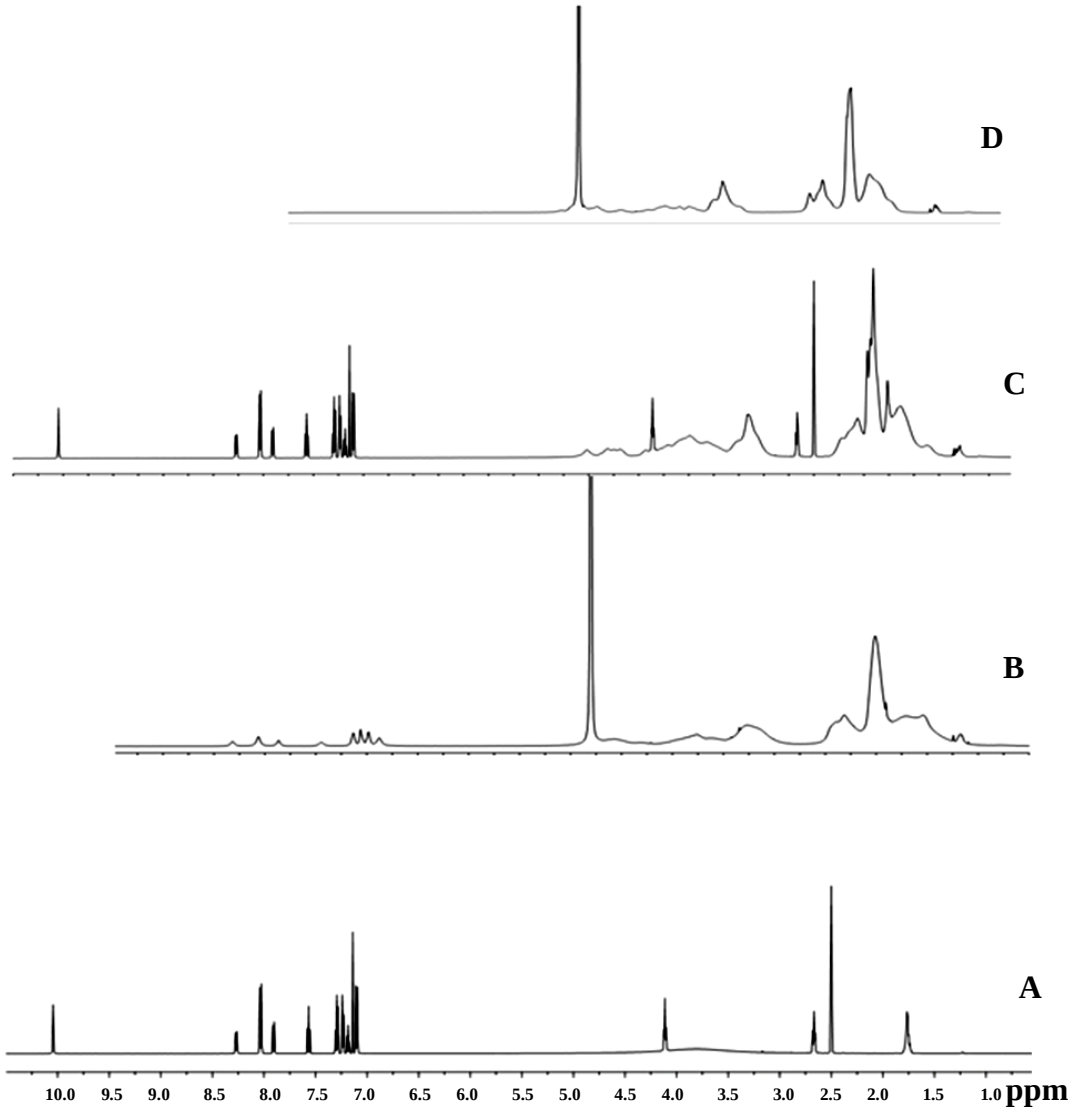
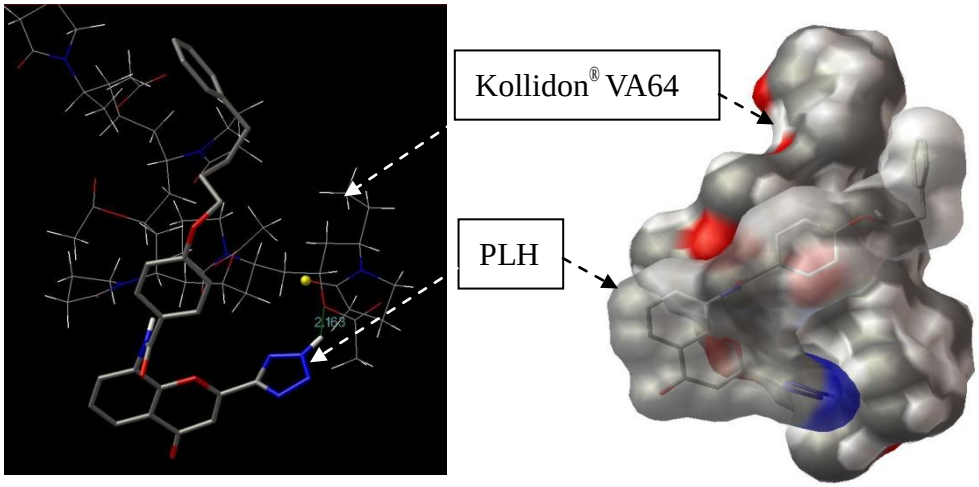


Figure 8. ^{1}H NMR spectra of the A. pure PLH in DMSO-d6, B. PLH :Kollidon® VA64: Na_2CO_3 (1:5:0.2) in D_2O, C. PLH: Kollidon® VA64, 1:5, in DMSO-d6, D. pure Kollidon® VA64 in D_2O. (0-14 ppm)



9 (A) **9 (B)**

Figure 9. Molecular simulation study for (a) the formation of hydrogen bond between PLH and Kollidon® VA64, and (b) molecular surface picture of PLH and Kollidon® VA64.

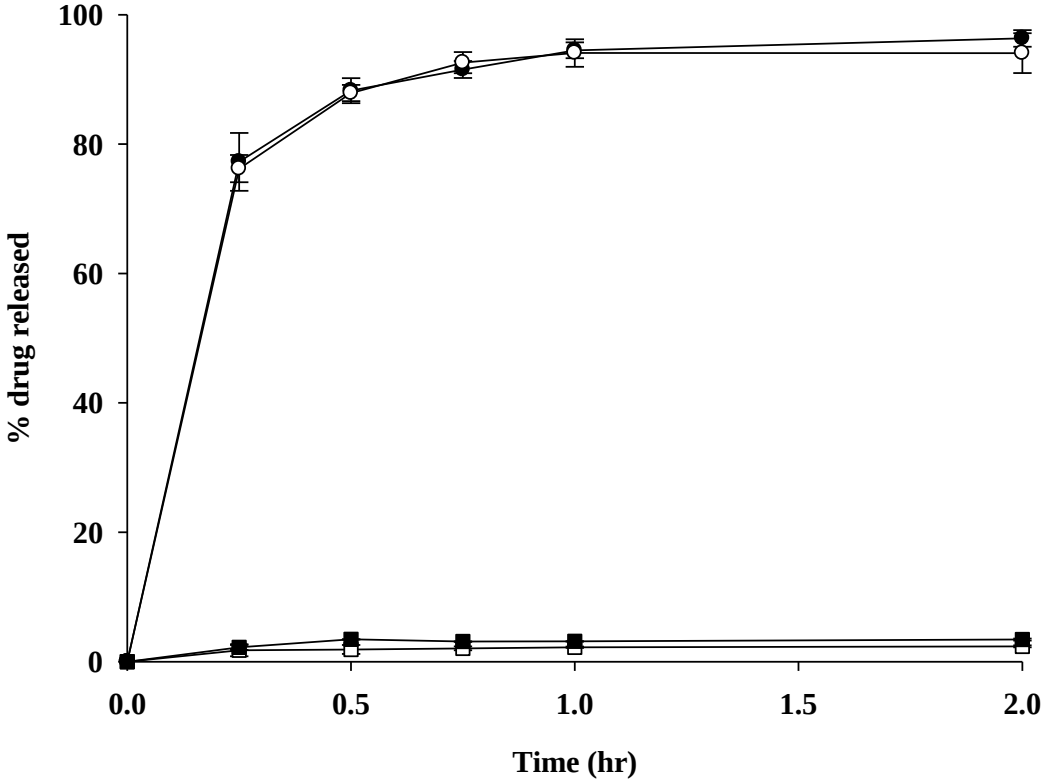


Figure 10. Dissolution profile of immediate release PM tablet (●), SD tablet (○), Onon® capsule (□), pure PLH (■) in pH 6.8 buffer (mean ± SD, n=3).

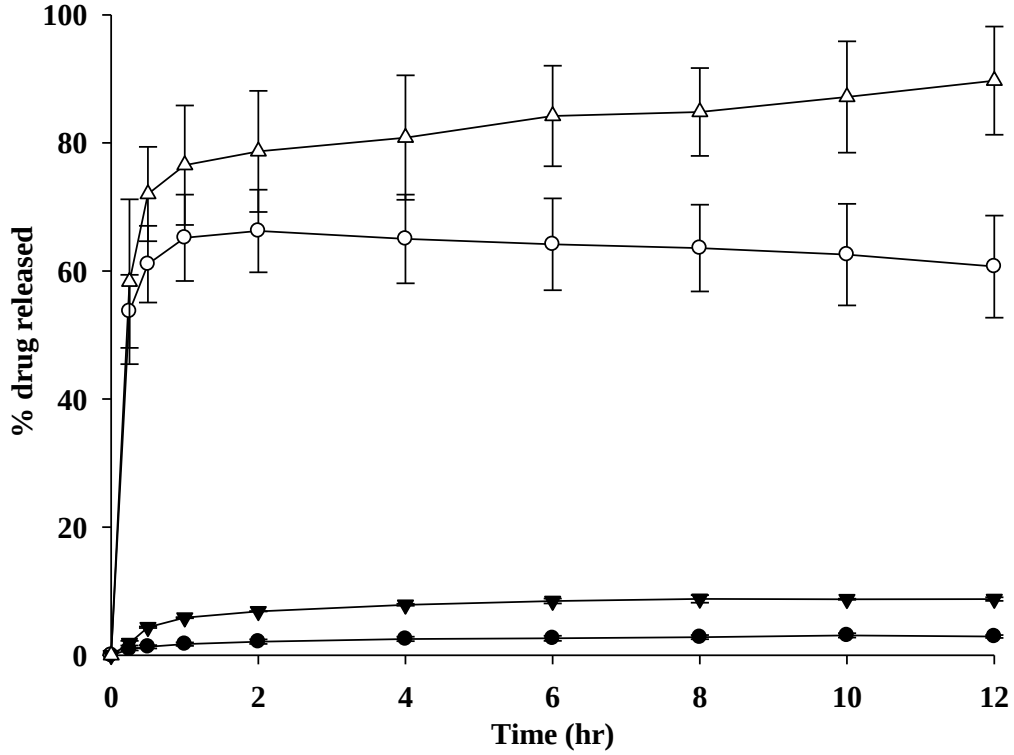


Figure 11. Dissolution profile of tablets with PLH (●), PLH: KollidonVA64, 1:2 (▼), PLH:Na_2CO_3, 1:0.2 (○), PLH:Kollidon® VA64:Na_2CO_3, 1:2:0.2 (Δ) in deionized water (mean ± SD, n=3).

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Oral formulation comprising pranlukast and hydrophilic polymer improved dissolution of poorly soluble drug through simple mixing process. **(**Applied for K

orean patent, October, 2012).

T. Ahmed, G-J. Lee, H-K. Choi, Enhancement of solubility and dissolution of poorly soluble drug pranlukast, AAPS Annual Meeting & Exposition at McCormick Place, Chicago, USA, October 14–18, 2012.

Gyeong-joo Lee, Taksim Ahmed, Hoo Kyun Choi, Strategies to improve solubility and dissolution of poorly soluble pranlukast, International conference of the Korean Society of Pharmaceutical science and Technology, Gwangju, Republic of Korea, November 29-30, 2012. (Best poster award)

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Taksim Ahmed
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College of pharmacy,
Chosun University, Gwangju,
Republic of Korea.