LIQUISOLID TECHNIQUE FOR IBUPROFEN TABLET

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Article Received on: 02/08/13 Revised on: 21/08/13 Approved for publication: 23/08/13

DOI: 10.7897/2230-8407.04926

IRJP is an official publication of Moksha Publishing House. Website: www.mokshaph.com

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ABSTRACT

Ibuprofen is a drug with poor solubility in water but good permeability in the gastrointestinal tract. Lquisolid tablet is one method of increasing solubility and dissolution rates of ibuprofen. The aim of this study is to determine the effects of glycerine, PEG 400, and propylene glycol as a non-volatile solvent and HPMC K4M as a hydrophilic polymer in order to understand the dissolution rates of ibuprofen lquisolid tablets. In this research, 10 formulas of ibuprofen lquisolid tablets were made. The ratio of ibuprofen in glycerine is 3:1; in PEG 400 and in propylene glycol is 5:1 with various concentration of HPMC K4M (2.5, 5 and 10 %). Formula non lquisolid was made as a control, so there was no addition of non-volatile solvent and hydrophilic polymer. Based on the results, ibuprofen lquisolid tablets that use glycerine, PEG400 or propylene glycol as the non-volatile solvent and HPMC K4M as the hydrophilic polymer can increase the dissolution rate constant of ibuprofen compared with non lquisolid ibuprofen tablets. The addition of HPMC K4M can increase the dissolution rate constant of ibuprofen lquisolid tablets until concentration of less than 2.5 % in glycerine; in PEG 400 can increase the dissolution rate constant of ibuprofen lquisolid tablets until concentration up to 5 % and in propylene glycol can increase the dissolution rate constant of ibuprofen until concentration up to 10 % because the polymer will swell and form a viscous layer that inhibits the disintegration; therefore, the percent release is decreasing.

Keywords: Ibuprofen, lquisolid, non-volatile solvent, hydrophilic polymer

INTRODUCTION

Ibuprofen is one of the drugs belonging to the NSAIDs (non-steroidal anti-inflammatory drugs) class, propionic acid derivatives having pharmacological effects as an anti-inflammatory, analgesic and antipyretic. Ibuprofen has poor solubility in water or practically insoluble in water.¹ To formulate a drug with a low level solubility in water. Many methods that can be done to help improving the dissolution rates of low solubility drugs are by reducing the particle size to increase the surface area; therefore, increasing the drug dissolution, dissolving the surfactant, formatting water- soluble complex will make derivatives in the form of the drugs that usually have higher dissolution and will lower the crystallization of the drugs through the form of solid solution. The most frequently used method is to increase the drug surface area using micronization (particle size reduction). However, this method often yields disappointing results especially when molded into tablets and encapsulated. Micronization drugs also have a tendency to form agglomerates due to hydrophobic properties and will reduce its surface area.² Currently, the lquisolid technique is one of the most promising methods to improve the dissolution rates of the drugs with low solubility in water. This technique is easy due to the relatively low cost and can be used in an industrial scale.³ Lquisolid technique is created by dissolving the active ingredient, which is lipophilic or poorly soluble in water, on non-volatile solvents such as propylene glycol, polyethylene glycol (PEG) 200 and 400, glycerine, polysorbate 80; or a suspension or liquid form which is then converted into an easy flowing powder form, non-adherent and ready to be compressed after the addition of the carrier and the coating material.⁴ Lquisolid technique has been demonstrated to increase the rates of drug dissolution of poorly soluble lipophilic drugs in water in small doses. However, for large dose of active ingredient, this type of formulation may proven to be impractical as the addition of carrier and coating materials will make the tablet

so big so that makes it difficult to swallow. In fact, if the therapeutic dose over 50 mg, increasing the dissolution rates by adding solvents, carriers and a small amount of coating materials is insignificant. However, at least one recent paper by Javadzadeh⁵, was able to formulate a big dose of carbamazepin as an active ingredient, PEG 200 as the non-volatile solvent and using some of the polymers which are PVP, HPMC and PEG 35 000 in the liquid dosage form. It would be possible to produce dry powder with a large content of active ingredients (carbamazepin). The investigators showed that the mixture of PEG 200 as the non-volatile solvent with PVP as the polymer showed the best dissolution rates compared with a mixture of PEG 200 and PEG 35000 HPMC as the polymer. Based upon the rates of dissolution testing of solvent of the tablets, lquisolid drug is better than the regular tablet (non-lquisolid). Additionally, our recent study has shown that ibuprofen lquisolid tablets that use glycerine or propylene glycol as the non-volatile solvent and PVP K-30 as the hydrophilic polymer can increase the dissolution rate constant of ibuprofen lquisolid tablets compared with ibuprofen conventional tablets (non-lquisolid).⁶ The addition of PVP K-30 as the hydrophilic polymer can increase the dissolution rate constant of ibuprofen lquisolid tablets until certain concentration; the polymer will swell and form a viscous layer which inhibits the disintegration, thereby allowing the percent release to decrease decreasing. The purpose of this study is to determine the *in-vitro* release profile of ibuprofen lquisolid tablet dosages by using three kinds of non-volatile solvents, namely glycerine, PEG 400 and propyleneglycol with HPMC K4M as the hydrophilic polymers compared to the conventional ibuprofen tablets as well as to determine the effects of hydrophilic polymer addition, HPMC K4M, and the effects of dissolution rate constant of ibuprofen lquisolid tablets with glycerine / PEG 400 / propyleneglycol as the non-volatile solvent.

MATERIALS AND METHODS

The following is the instruments used in this research. Single punch tablet molding machine (TDT model, Shanghai, China); tablet hardness tester (Schleuniger 6D type-30, Germany); tablet friability tester (Erweka type TA-3, Germany); tablet disintegration tester (Erweka type ZT3-1, Germany); tablet dissolution tester (Erweka type DT-70, Germany); spectrophotometer UV-VIS (Hitachi type U-1100, Japan); stopwatch (Herwina type NR 47 727, Switzerland). The materials which have pharmaceutical grade specifications used in this research are ibuprofen (Shasun Chemicals and Drugs, Ltd.), Glycerine, PEG 400, Propylenglycol, HPMC K4M, Avicel PH 102, Aerosil PH 102, Sodium starch glycolate and Magnesium Stearate. Nine liquisolid systems of ibuprofen (denoted as LS-1 to LS-9) were prepared and compressed into cylindrical tablets which consisted of 200 mg each tablet using the single punch tablet machine. The Formulas of ibuprofen liquisolid tablets are listed on Table 1. Evaluation of liquisolid powder and tablets were examined; moreover, the evaluation of powder was based upon Carr's index and Hausner ratio. The evaluation of the tablets included weight uniformity, content uniformity, hardness, friability, disintegrating time and drug content uniformity. 20 tablets were taken randomly and after that the tablets were finely ground and stirred until homogeneous. Then, the equipment of 800 mg sample with 200 mg ibuprofen were carefully weighted and were dissolved into 0.2 M phosphate buffer solution with pH 7.2 for serving 100.0 mL flask. They were all shaken until in the state of homogeneous. After that, they

were filtered with Whatman filter paper. The first filtration screening result was discarded, then a volume of 1.5 mL was pipetted and mixed with a solution of 0.2 M phosphate buffer, pH 7.2, until the appropriate volume reached 10 mL. Observations of the wave length absorbance of maximum absorptions were conducted using UV-VIS spectrophotometer using the maximum absorption wave length of 264 nm. The test was performed on the prepared ibuprofen liquisolid tablets according to the USP XXVIII⁷ dissolution procedures, apparatus 2. The tablet was inserted into a flask containing solution of 0.2 M phosphate buffer with pH 7.2 which served as a medium. The paddle was rotated at 50 rpm velocity. Medium temperature was maintained constantly $37 \pm 0.5^\circ\text{C}$ with 900-mL volume of dissolution medium which was used. Samples of 5 mL were withdrawn at regular time intervals of 10, 20, 30, 45 and 60 minutes. The number of medium was replaced with new medium drawn by the same amount, so that the volume of the medium was always constant. Each sample taken from the dissolution medium was filtered and analyzed spectrophotometrically at 264 nm. Dissolution rate constant values shown on the graph were from the relationships between remaining drug percentage versus time, while the Dissolution Efficiency (DE) at 60 minutes for each tablet formula was obtained through the equation according to the method of Khan.⁸ Dissolution rate constant values and the Dissolution Efficiency (DE) at 60 minutes were statistically analyzed using one way ANOVA method using significant level of $p < 0.05$.

Table 1: The Composition Formula of Ibuprofen Liquisolid Tablets

Liquisolid Systems	Non Volatile Solvents	Hydrophilic Polymer	Drug Concentration in Liquid Medication (% w/w)	R	Lf	Tablet weight (mg)
Non LS	-	-	-	-	-	800
LS-1	glycerine	6.67	75	25	0.58	800
LS-2	glycerine	13.33	75	25	0.59	800
LS-3	glycerine	26.67	75	25	0.60	800
LS-4	PEG-400	6	83	24	0.53	800
LS-5	PEG-400	12	83	24	0.53	800
LS-6	PEG-400	24	83	24	0.55	800
LS-7	Propylene glycol	6	83	25	0.49	800
LS-8	Propylene glycol	12	83	25	0.50	800
LS-9	Propylene glycol	24	83	25	0.51	800

Table 2: Evaluation of Ibuprofen Liquisolid Powder and Tablets

Formula	Carr's Index (%) $\pm$ SD	Hausner Ratio $\pm$ SD	Hardness (Kp) $\pm$ SD	Friability (%) $\pm$ SD	Disintegration Time (min) $\pm$ SD
Non LS	18.33 $\pm$ 1.53	1.22 $\pm$ 0.02	13.25 $\pm$ 0.44	0.1 $\pm$ 0.04	0.23 $\pm$ 0.08
LS-1	14.00 $\pm$ 1.00	1.16 $\pm$ 0.02	12.80 $\pm$ 0.08	0.08 $\pm$ 0.04	1.42 $\pm$ 0.11
LS-2	12.67 $\pm$ 1.53	1.14 $\pm$ 0.02	13.15 $\pm$ 0.03	0.08 $\pm$ 0.04	1.69 $\pm$ 0.31
LS-3	14.00 $\pm$ 1.00	1.16 $\pm$ 0.02	12.91 $\pm$ 0.09	0.08 $\pm$ 0.04	2.18 $\pm$ 0.03
LS-4	18.16 $\pm$ 0.76	1.22 $\pm$ 0.02	7.57 $\pm$ 0.26	0.12 $\pm$ 0.06	1.30 $\pm$ 0.11
LS-5	18.91 $\pm$ 0.15	1.23 $\pm$ 0.00	7.42 $\pm$ 0.18	0.16 $\pm$ 0.07	1.41 $\pm$ 0.10
LS-6	18.99 $\pm$ 0.01	1.23 $\pm$ 0.00	7.45 $\pm$ 0.27	0.10 $\pm$ 0.04	1.51 $\pm$ 0.09
LS-7	18.33 $\pm$ 1.53	1.20 $\pm$ 0.01	12.98 $\pm$ 0.54	0.10 $\pm$ 0.09	1.72 $\pm$ 0.23
LS-8	18.97 $\pm$ 2.62	1.22 $\pm$ 0.00	12.96 $\pm$ 0.52	0.10 $\pm$ 0.09	2.26 $\pm$ 0.24
LS-9	16.99 $\pm$ 0.01	1.20 $\pm$ 0.01	12.94 $\pm$ 0.33	0.08 $\pm$ 0.07	2.30 $\pm$ 0.05

Table 3: The Weight and Assay of Ibuprofen Liquisolid Tablets

Formula	Weight of Tablets (%) $\pm$ SD	Assay of Tablets (%) $\pm$ SD
Non LS	100.71 $\pm$ 0.80	99.91 $\pm$ 1.12
LS-1	100.12 $\pm$ 0.66	100.17 $\pm$ 0.14
LS-2	100.16 $\pm$ 0.86	100.28 $\pm$ 0.11
LS-3	101.02 $\pm$ 0.59	100.23 $\pm$ 0.21
LS-4	99.68 $\pm$ 0.60	99.42 $\pm$ 0.66
LS-5	99.72 $\pm$ 0.43	99.58 $\pm$ 0.23
LS-6	99.53 $\pm$ 0.60	99.61 $\pm$ 0.48
LS-7	99.71 $\pm$ 0.46	99.94 $\pm$ 0.65
LS-8	99.42 $\pm$ 0.61	99.84 $\pm$ 0.85
LS-9	99.38 $\pm$ 0.68	99.93 $\pm$ 0.90

Table 4: The Result of Dissolution Test of Ibuprofen Liquisolid Tablets

Formula	Dissolution Efficiency $\pm$ SD	Dissolution rate (minute ⁻¹) $\pm$ SD
Non LS	73.20 $\pm$ 0.24	0.0192 $\pm$ 0.00
LS-1	81.37 $\pm$ 0.59	0.0309 $\pm$ 0.00
LS-2	86.59 $\pm$ 0.21	0.0428 $\pm$ 0.00
LS-3	82.86 $\pm$ 0.28	0.0356 $\pm$ 0.00
LS-4	83.80 $\pm$ 0.50	0.0700 $\pm$ 0.01
LS-5	78.21 $\pm$ 0.06	0.0687 $\pm$ 0.00
LS-6	73.53 $\pm$ 0.38	0.0605 $\pm$ 0.01
LS-7	82.96 $\pm$ 0.12	0.0231 $\pm$ 0.01
LS-8	81.44 $\pm$ 0.38	0.0348 $\pm$ 0.00
LS-9	87.15 $\pm$ 1.52	0.0278 $\pm$ 0.01

Figure 1: The dissolution profiles of Conventional Ibuprofen and Liquisolid Tablets with Phosphate Buffer 0.2 M pH 7.2

RESULTS AND DISCUSSION

Evaluation of Ibuprofen Liquisolid Powder and Tablets

Liquisolid powder quality testing's including angle of repose, Carr's index and Hausner ratio to determine the flow ability. The quality testing's of liquisolid powder and tablets are shown on Table 2. The result shows that the formula fulfills all the requirements according to Indonesian Pharmacopeia. This suggests that the liquisolid powder results posses good flow properties because each

formula using Avicel PH-102 can increase the flow rate and reduce tablet's weight variation.⁹ Liquisolid powder produced from liquisolid system (LS-1 – LS-9) has better flow properties than non-liquisolid formula (non LS); this proves that the system can improve the flow properties of liquisolid powder. Liquisolid powder flow properties greatly affect the uniformity of weights; and the good flow

properties of liquisolid powder will flow well into the tablet machine in order to obtain and ensure uniformity of weights filling productions. Hardness test results for all the formulas can be seen on Table 3 which demonstrates the difference in hardness between the formulas due to the composition of each formula is different. Friability test results (Table 3) show that the formula meets all the requirements of the friability of the tablets which are less than 1 %. It indicates that the tablet is able to overcome the shock and wear without being destroyed during the production process, packaging, and delivery to be used by consumers. The test results for all the disintegration time of tablet formulas (Table 3) meet the requirements of less than 15 minutes.¹⁰ Time difference in each formula can be destroyed due to a difference in the composition of the tablets. Although all the formulas containing Avicel PH 102 which is hydrophilic, the formula non LS contains no HPMC K4M polymer; therefore, the destruction works rapidly, while another formula containing HPMC K4M polymer shows a number of increases from 1.3 to 2.3 minutes. Increasing the amount of polymers in the formula is very influential at the time of destructions; the amount of HPMC K4M in the formula LS-3, LS-6, and LS-9 shows much longer time of destructions than most other formulas. This is due to the addition of HPMC K4M in considerable numbers to form a thick layer around the tablet upon contact with water tablets; the tablets crushed and made the process slower. Test results of the weight uniformity and assay of tablets (Table 3) indicate that the formula meets all the requirements. The amount of active ingredients from each of 10 dosage units lies between 85.0 % and 115.0 % which are listed on the label with variation coefficient of less than 6.0 %.¹¹ It is proven that the powder can flow liquisolid properly to fill the print space in order to produce tablets and have weight tablet uniformity and content diversity which are good.

***In-vitro* Dissolution Studies**

Based on the data and release profile of ibuprofen liquisolid tablet (Figure 1) and the ED60 (%) (Table 4), the tables and figure show when compared with formula non LS, the formula LS-1 and LS-2 use glycerine as the solvent; formula LS-IV uses PEG 400 as the solvent; the formula LS-7, LS-8, and LS-9 use propylene glycol as the solvent show an increase in percentage of drug released. However, the formula LS-3, LS-5, and LS-6 demonstrate a decrease in percentage of the drug released. Formula LS-1 and LS-2 have a higher percent release compared with the formula non LS, whereas the release of the formula LS-3 has the lowest percent. This is due to formula non LS that contains no solvents and polymers which can help improve the solubility, while the formula LS-1 and LS-2 contain glycerine as the solvent and HPMC K4M as the polymer to increase concentrations. However, the formula LS-3 which contains the amount of HPMC K4M at most (10 % of the liquid medication) has low percent at its disposal; this is due to the broken formula LS-3 which is longer than the formula LS-1 and LS-2. It is influenced by the enough addition of HPMC K4M formula, so that when contact with water, the polymer will expand and form a thick layer that inhibits the release of disintegration; therefore, it lowers the percentage. Percent drug releases of formula LS-1 to LS-9 are higher than the formula non LS. This indicates that the liquisolid system

can improve drug dissolution, and if viewed per cent of drug release the 10th minute, another formula which has a drug release percent higher than the formula non LS shows that the liquisolid system used allowing the onset of drug action quicker, so it would be faster to give effect to patients. An increased number of drugs can be seen in a profile that uses glycerine as the solvent as used by formula LS-1 and formula LS-2 which are formulated by using the liquisolid technique when compared with formula non LS. However, formula LS-3 shows a decrease in the amount of drug release when compared with formula LS-2. An increased amount of drug release of formula LS-4 can be seen in a profile that uses PEG 400 which formulated using the liquisolid technique when compared with formula non LS; however, formula LS-5 and LS-6 demonstrate a decline in the amount of drug release when compared with formula LS-4. Profile that uses propylene glycol as the solvent shows an increased amount of drug release as shown by formula LS-7, LS-8, and LS-9 which are formulated by using the liquisolid technique when compared with formula non LS. The results of dissolution rate constant calculations (Table 4) show that all the formulas used liquisolid system have a higher dissolution constant value than the formula I. This proves that the liquisolid system can improve the drug dissolution constant rates. Dissolution rate is a determinant of the absorption stage. By understanding the rates of dissolution, absorption rate can be expected to affect the early work, intensity, and duration of drug action in the body. In a formula using HPMC K4M with concentration of 10 % (LS-3, LS-6, and LS-9), it appears a decrease in the dissolution rate constant values; this is due to the higher viscosity layer at the time of the drug in contact with water, and it will be a barrier to drug release.

CONCLUSION

In conclusion, ibuprofen liquisolid tablets that use glycerine, PEG 400, and propylenglycol as a non-volatile solvent and HPMC K4M as a polymer can enhance the dissolution rates of ibuprofen liquisolid tablets better than conventional technique (non-liquisolid). The addition of hydrophilic polymer, HPMC K4M and a non-volatile solvent, glycerine can increase the dissolution rates; polymer concentration which is more than 5 % will expand and form a thick layer that inhibits the release of disintegration, so that the percent is decreasing. However, the addition of hydrophilic polymer, HPMC K4M and a non-volatile solvent, PEG 400 can enhance the dissolution rates; polymer concentration which is greater than 2.5 % will swell and form a thick layer that inhibits the release of disintegration, so that the percent is decreasing, while the addition of hydrophilic polymer HPMC K4M and a non-volatile solvent, propylene glycol can enhance the dissolution rates of ibuprofen liquisolid tablets.

REFERENCES

1. Sweetman SC. Martindale. The complete drug reference; 36thed. London: The Pharmaceutical Press; 2009.
2. Javadzadeh Y, Siahi Shadbad MR, Asnaashari S, Nokhodchi A. Liquisolid Technique as a Tool for Enhancement of Poorly Water-Soluble Drugs and Evaluation of Their Physicochemical Properties. *Acta Phar* 2007; 57: 99–109. <http://dx.doi.org/10.2478/v10007-007-0008-6> PMID:19839410
3. Yadav VB, Yadav AV. Liquisolid Granulation Technique for Tablet Manufacturing: an Overview. *Journal of Pharmacy Research* 2009; 2(4): 670-674.
4. Gubbi S, Jarag R. Liquisolid Technique for Enhancement of

- Dissolution Properties of Bromhexine Hydrochloride. *J. Pharm* 2009; 2(2): 382–386.
5. Javadzadeh Y, Navimipour BJ, Nokhodchi A. Liquisolid Technique for Dissolution Rate Enhancement of a High Dose Water Insoluble Drug (Carbamazepine). *International Journal of Pharmaceutics* 2007^b; 341: 26–34. <http://dx.doi.org/10.1016/j.ijpharm.2007.03.034> PMID: 17498898
 6. Hadisoewignyo L, Hadi E, Wibowo N. Liquisolid Ibuprofen Tablets. *Indonesia Journal of Pharmacy* 2011; 22(3): 204–211.
 7. The United State of Pharmacopeia XXVIII, The National Formulary 23. US Pharmacopeial Convention, Inc., Mack Publishing Co., Easton; 2005.
 8. Khan KA. The Concept of Dissolution Efficiency. *J. Pharm* 1975; 27(1): 48–49. <http://dx.doi.org/10.1111/j.2042-7158.1975.tb09378.x>
 9. Ohwoavworhua FO, Adelakun TA, Okhamafe AO. Processing Pharmaceutical Grade Microcrystalline Cellulose from Groundnut Husk: Extraction Methods and Characterization. *International Journal of Green Pharmacy* 2009; 3(2): 97–104. <http://dx.doi.org/10.4103/0973-8258.54895>
 10. Indonesian Pharmacopeia. 3rd ed. Jakarta: Ministry of Health Republic of Indonesia; 1979.
 11. Indonesian Pharmacopeia. 4th ed. Jakarta: Ministry of Health Republic of Indonesia; 1995.

Cite this article as:

Hadisoewignyo Lannie, Dewi Linda Purnama, Mellisa Fenny, Jojana Tallisa. Liquisolid technique for ibuprofen tablet. *Int. Res. J. Pharm.* 2013; 4(9):123-127 <http://dx.doi.org/10.7897/2230-8407.04926>

Source of support: Nil, Conflict of interest: None Declared