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The Effect of Solid Dispersion Methods on the Dissolution Profile of Meloxicam

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Abstract : Solid dispersion is a homogeneous mixture of one or more active substances in an inverse matrix to get better dissolution and bioavailability from water insoluble active substances. Meloxicam as water insoluble inactive substances is used as a rheumatoid arthritis therapy, osteoarthritis from oxicam derivatives. As a Class II compound on a Biopharmaceutical Classification System (BCS) with low dissolution in digestive system. Solid dispersion of meloxicam is made of various methods and its applications (M1, M2, M3, M4, M5 and M6) using polymers PEG 6000 and PVP K30. Comparisons between polymer and meloxicam are 1:2 (F1), 1:4 (F2) and 1:8 (F3). The parameters used from dissolution profile are solubility (Q), the area under the curve (AUC) and dissolution efficiency (DE) which are measured on a 60 minute process of dissolution. Solid dispersion powder, physical mixtures and pure meloxicam are characterized by Fourier Transform Infra Red (FTIR), Differential Scanning Calorimetry (DSC) and X-ray diffraction.The results showed that of dissolution profile for each method and the best applications were M3F3 formula (Q = 103.90%; AUC = 2983.48; DE = 99.45%), M5F2 formula (Q = 98.14%; AUC = 2606.56; DE = 86.89%) and M6F3 formula (Q = 79.68%; AUC 2009.85; DE = 67.00%) Statistically, one-way ANOVA test showed that there were differences in the methods of dissolution profile of meloxicam and the applications of solid dispersion ($p < 0.05$). Therefore, it was concluded that from the method and applications of solid dispersion of meloxicam, formula M3F3 was the best method and the best application to improving the dissolution profile of meloxicam in a solid dispersion system.
Keywords: *Solid dispersion, PEG 6000, PVP K30, Meloxicam, Disolusi.*

Introduction:

Improved dissolution of a drug is very important to improve the bioavailability of the drug in the blood. Drugs with a small dissolution means to have a little water solubility and absorption small. Efforts to promote the dissolution can be applied several methods such as modifying the physical properties, the addition of solubility-enhancing ingredients, reduce the size of the particle, nanosuspensi technology, adjusting the pH and solid dispersion system[1].

Solid dispersion is a homogeneous mixture of one or more active substances in a carrier that is inert to obtain dissolution and bioavalabilitas better than the active substance poorly soluble in water[2]. The solid dispersion system based on the concept that the ingredients dispersed in a polymer carrier or inert, usually used methyl cellulose, urea, lactose, citric acid, polivenil pyrrolidone (PVP), polyethylene glycol (PEG) 4000 or 6000, etc.[3]. Improved dissolution of a drug in solid dispersion system is influenced by the selection method of manufacture, the types and proportions of polymers[4]. The success in increasing dissolution of the results of research, especially in solid dispersion system has been widely applied, especially for drugs with solubility

values in the gastrointestinal fluid is low or in the Biopharmaceutical Classification system (BCS), including the class II and class IV.

Meloxicam with chemical formula $C_{14}H_{13}N_3O_4S_2$, including the class II on the BCS system. Has a low solubility or practically insoluble in water, meaning that one part of a substance can be dissolved in at least 10,000 parts solvent (1:> 10000). Very slightly soluble in alcohol, slightly soluble in acetone. Meloxicam is one of Non-steroidal Anti-Inflammatory drugs (NSAIDs) derivative oksikam. Used in the treatment of rheumatoid arthritis, osteoarthritis and other joint diseases. The use of orally at a dose of 15 mg per day as a single dose may increase the risk of gastrointestinal disorders, dyspepsia, diarrhea, gastrointestinal infections. Peak plasma levels achieved after the 6 hours of oral administration and rectal [5].

Experimental

Equipmens/Material:

Glassware laboratory standards, analytical balance (BOECO), pH meter (ATC Hanna Instruments), water bath, drying cabinets, thermometer, desiccator, sieve of 80 mesh, sonicator, magnetic stirrer, mixer, stopwatch, spectrophotometers infrared (FT-IR SHIMADZU IR Prestige-21), diffraction X (Shimadzu XRD-6100), dissolution tester, Spectrophotometer UV-Vis (Shimadzu 1800 UV spectrophotometer), Differential Scanning Calorimeter (SDTQ 600).

Materials used were meloxicam (Swati Spentosepvt.Ltd, Gujarat India) from PT. Tatarasa Primatama, polyethylene glycol (PEG) 6000 and polivenil pyrrolidone (PVP) K30 (BASF, Germany) from CV. Primary Global Science, ethanol (96%), distilled water, phosphate buffer pH 7.5.

Preparation of solid dispersions

Solid dispersion powder prepared in accordance with formulations such as Table.1

Table.1 Formulation of solid dispersions and physical mixtures

NO	Method/polymer	Treatment	Formulation (Drug-polymer)		
			F1(1:2)	F2(1:4)	F3(1:8)
1	Melting method/ Polymer PEG6000	M1	M1F1	M1F2	M1F3
2		M2	M2F1	M2F2	M2F3
3		M3	M3F1	M3F2	M3F3
4	Solvent method/ Polimer PVP K30	M4	M4F1	M4F2	M4F3
5		M5	M5F1	M5F2	M5F3
6	Melting-solven method/ Polimer PEG6000	M6	M6F1	M6F2	M6F3
7	Physical mixture (adapted to the method)	M7	M7F1	M7F2	M7F3
8		M8	M8F1	M8F2	M8F3

M1: Solution ingredients added to the polymer solution
M2: Material medicine was added into molten polymer
M3: A mixture of the drug and polymer were both melted
M4: Material drug dissolved in a solvent, the polymer was added
M5: Material drug and polymer ware dissolved in a solvent, mixed
M6: reconstituted drug material with a solvent added to the polymer melt
M7: physical mixture of drug and polymer (polymer on melting)
M8: physical mixture of drug and polymer (polymers on dissolution)
F1: Formula 1
F2: Formula 2
F3: Formula 3

Determination of the wavelength of maximum absorption meloxicam and manufacture calibration curve:

Carefully weighed 50 mg meloxicam, was put into a flask of 100 ml, was added 6 ml of methanol and 1.5 ml of 0.1 N NaOH and diluted with phosphate buffer pH 7.5 to the line mark. The solution was sonicated for 5 minutes and filtered. The filtrate pipette 3 ml and diluted with phosphate buffer pH 7.5 to 100 ml in order to get the levels of 15 ug / ml. The solution had an absorbance was measured in a spectrophotometer UV-Vis absorption at a wavelength of 200-400 nm. Then do manufacture calibration curve and equation: $y = a + bx$

The dissolution test meloxicam solid dispersion powder:

Using a type 2 dissolution apparatus (type rower) for 60 min, 37 ± 0.5 °C, pH 7.5 phosphate buffer medium of 900 ml. The dissolution test carried out on a solid dispersion powder equivalent to 50 mg of meloxicam. Tools run with a speed of 100 rpm. Dissolution fluid 5 ml pipette minute intervals-5, 10, 15, 30, 45 and 60. The absorbance was measured by UV-Vis spectrophotometer at the wavelength of maximum absorption.

X-ray diffraction test:

Samples were placed in the sample holder and leveled. The analysis was made on the 10-70 degree range, speed of 2 degree / min. At the peak diffractogram appear in units of deg (degree) and the intensity cps (counts per second) as the unit of emissions.

Test FT-IR (Fourier Transform Infra Red):

Infrared spectrophotometer using KBr discs. Weighed each sample (2-3 mg) and dispersed in KBr (400 mg). Absorption spectra were recorded in the value of 4000-500 cm^{-1} with a resolution of 4 cm^{-1}.

Test DSC (Differential Scanning Calorimetry):

DSC thermal test carried out on the powder (10 mg) was inserted into the container platinum, leveled and then heated 20-300^{o}C with nitrogen 100 ml per min at a speed of 10 °C per minute.

Results and Discussion

Determination of the maximum wavelength of meloxicam in pH 7.5 phosphate buffer solution absorbance values obtained maximum at 362 nm and a calibration curve with the equation:

$y = 0.04639 (x) + 0.001092$; with the value of $r = 0.9997$. Values obtained equation shows a linear relationship between absorbance and concentration.

The application of different methods that provide different solutions. The fusion method (M1, M2, M3) where the application of the M1 (respectively melted, then mixed) can not be done. Meloxicam when heated to melt will change color from yellow to dark brown astray after the melt, so that the application of this method can not be continued. Application of M2 and M3, two different implementations provide a different dissolution profile, as well as the amount of polymer used (F1, F2 and F3). statistically one way ANOVA test (one way ANOVA) showed that there were differences in dissolution profiles ($p < 0.05$). In a further test Duncan dissolution profile M3F3 formula differ significantly from the other formulas, such as in Figure 1.

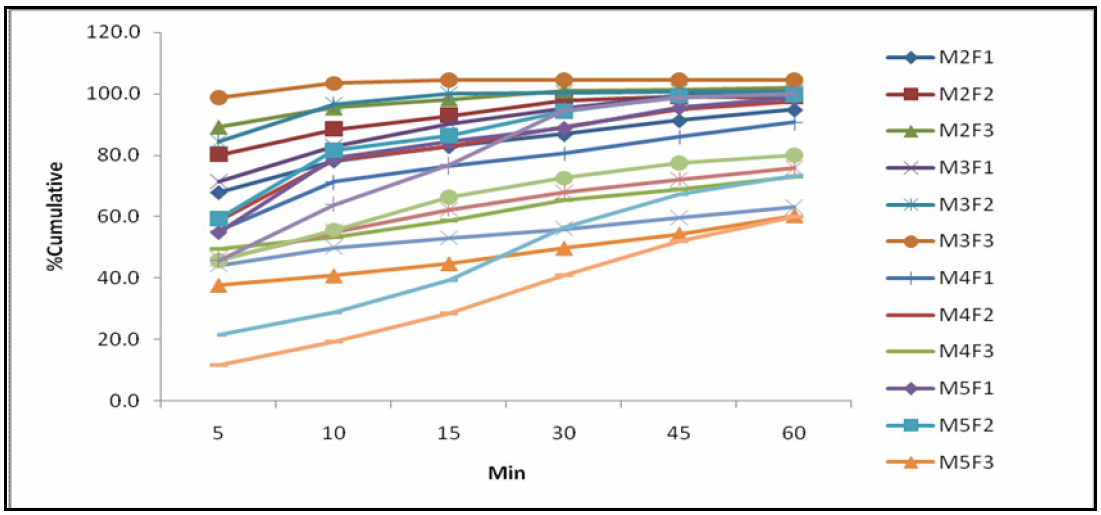

Fig 1. Chart of the cumulative percentage of dissolution meloxicam solid dispersion powder, drug-polymer physical mixture and pure meloxicam.

PEG 6000 as one polymer that is widely used in solid dispersion system, directly proportional to the amount of meloxicam dissolution profile,. Smelting smelting method with the application of PEG 6000 and meloxicam simultaneously, giving dissolution results were better than the application of meloxicam mixing into molten PEG 6000. Mixing the polymer resulted in a reduction ukuranpartikel. Results recrystallization of fused two substances very slowly due to changes in viscosity environment, this condition causes the particles formed smaller than the particles of pure compound so that the surface area increases. Besides the effect of PEG polymer solubility of meloxicam 6000 to also support increasing the dissolution rate [6; 7].

The process of formation of solid dispersions with polymer PVP K30 is the cloaking agent by the polymer particles, the formation of hydrogen bonds between the two substances so that the increased wettability of drug particles [7]. However, these polymers have limitations, PVP K30 on the amount that is too large can increase the viscosity of that substance meloxicam is difficult to separated from the polymer.

DSC measurement, one way to look at the melting point of a substance that is then related to changes in particle shape is intrinsically linked to the dissolution profile. As shown in Figure 2, the results of DSC analysis shows that the melting point of the polymer changes meloxicam and when the two substances are mixed, both solid dispersion system as well as a physical mixture.

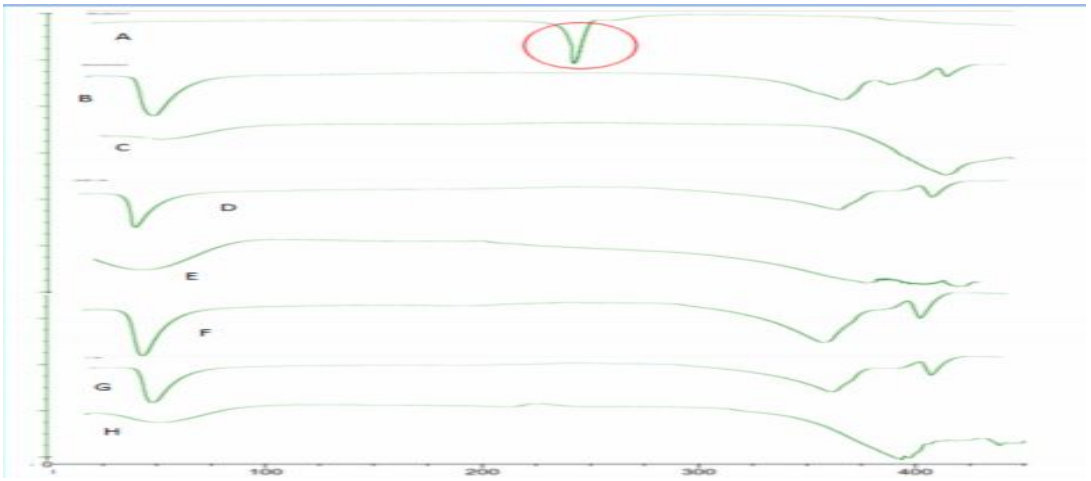

Fig 2. DSC thermogram (A) meloxicam, (B) PEG 6000, (C) PVP K30, (D) Solid dispersion M3F3, (E) Solid dispersion M5F2, (F) Solid dispersion M6F3 (G) physical mixture M7F3 and (H) physical mixture M8F2

The melting point of a mixture of meloxicam-PEG 6000 are lower than pure meloxicam. 258,07°C temperature changes occur of (pure) become 61,76°C solid dispersion formula 64,86°C M3F3 and temperature on physical mixture M7F3 formula. This suggests that the formation of meloxicam solid dispersion system which is then compacted by melting quickly in cold conditions proved capable of dispersing the drug particles with a smaller size into the polymer. In formula M3F3 endothermic peak is not so sharply compared with a physical mixture of meloxicam-PEG 6000 or by meloxicam itself. However sharper than the endothermic peak PEG 6000.

The same thing happened to the melting point of a mixture of meloxicam-PVP K30. In the polymer PVP K30 itself looks wide endothermic peak showing the amorphous state. In meloxicam and PVP K30 mixture of both solid dispersion system or a physical mixture shows that the endothermic peak of meloxicam did not look, which seemed only the endothermic peak of PVP K30. Loss of or reduction in the peak of the endothermic peak of a substance in another substance (polymer) indicates there has been a physical interaction as a consequence of the formation of the amorphous phase, resulting in downsizing [1]. Decrease the melting temperature of the system caused by the component substances that low melting temperature dynamically changes so it diffuses into the crystal lattice of substances [6].

The fall in melting a mixture of meloxicam (PEG 6000 and PVP K30) than the pure form of meloxicam showed that there had been interaction between meloxicam and polymers. This interaction causes the change in crystal form becomes amorphous so on calorimetry is not so visible exothermic peak. The shape change is the result of his energy (enthalpy) is required to melt the mixture than crystalline forms and calorimetry mix looks more ramps [8; 9].

Thermodynamic system can be considered as a mixture of two forms of the structure of the component substances. This is evident from the results of X-ray diffraction analysis, in Figure 3. The pattern meloxicam gives peaks typical interference, as well as PEG 6000 as crystalline polymers with a high degree of symmetry.

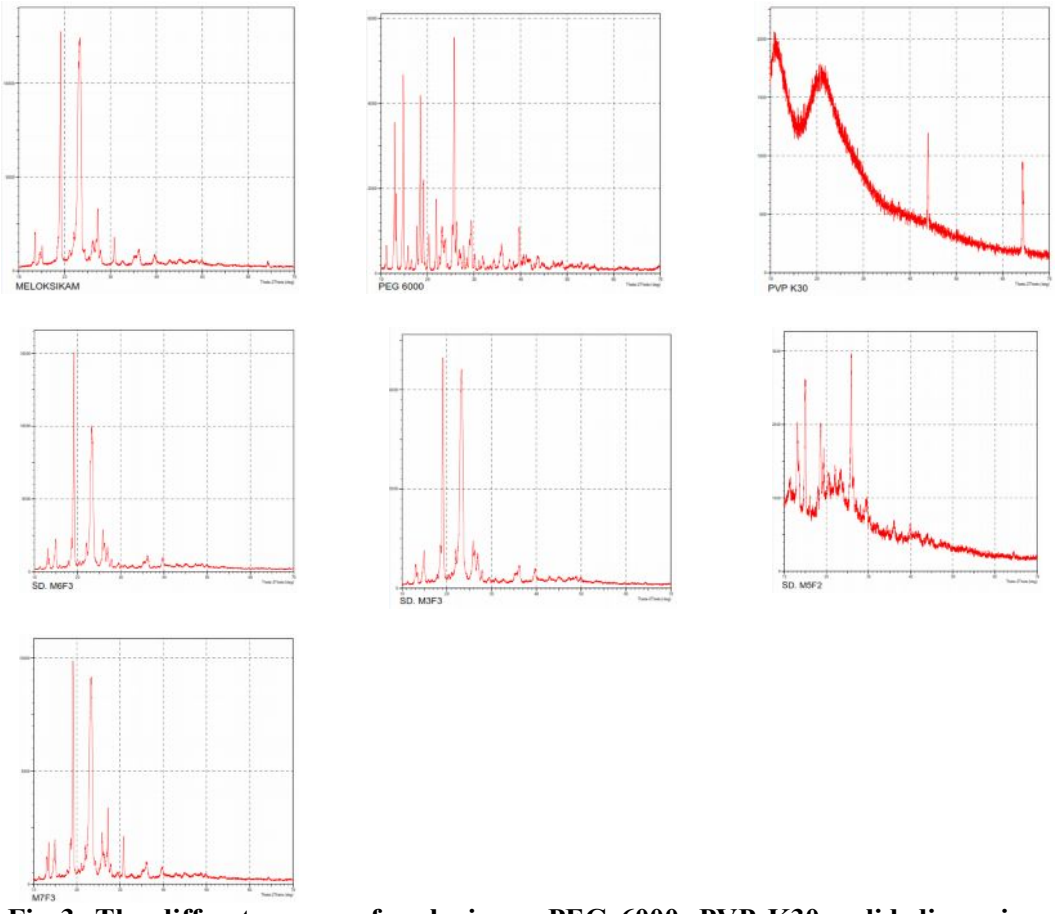

Fig 3. The diffractograms of meloxicam, PEG 6000, PVP K30, solid dispersion and physical mixture meloxicam-polymer

In the solid dispersion system diffraction patterns in certain areas sometimes do not appear, as shown in the diffraction pattern of the substance. In the solid dispersion formula M3F3 and M6F3, peaks should look at areas such as meloxicam 30 deg pure, but the peak is not visible. This indicates that the particles are formed into the molecular structure of the polymer particles. Likewise, upon mixing with the polymer PVP K30 meloxicam M5F2 formula diffraction pattern of polymer PVP K30 as an amorphous form which can reduce the intensity of meloxicam itself so that the mixing of the two substances showed that the crystalline forms of meloxicam decreases towards the amorphous form. Meloxicam diffractograms seen high peak intensity indicating that meloxicam is still in crystalline form. Meloxicam diffractograms solid dispersion system-polymer, showing the pattern of each peak interference of both components that appear in the area that are similar to the pattern of meloxicam but there is a change in the intensity of the peak.

Changes in the intensity decreased slightly in the diffraction pattern showed that there had been a change towards amorphous form. This happens on a physical mixture of drug-polymer, although the intensity of the peak is sharper than solid dispersion but lower than the peak diffractogram meloksikamnya sendiri.Intensitas describes the number of crystals in substance. The more phase crystals will be imaged with a sharp peak intensity and vice versa. The decrease in the peak intensity diffractogram patterns indicate changes to the amorphous crystalline form. The bond between the dye molecules to form crystals has been deformed by a molecular bond with the polymer molecular substances. The interaction between the molecules is reflected in the shift of absorption band of infrared spectrum analysis results [10].

FTIR spectra obtained from, in Figure 4. Where the absorption bands of drug compounds and polymers for solid dispersion and physical mixture still persists in the range of wave numbers the same as in pure meloxicam.

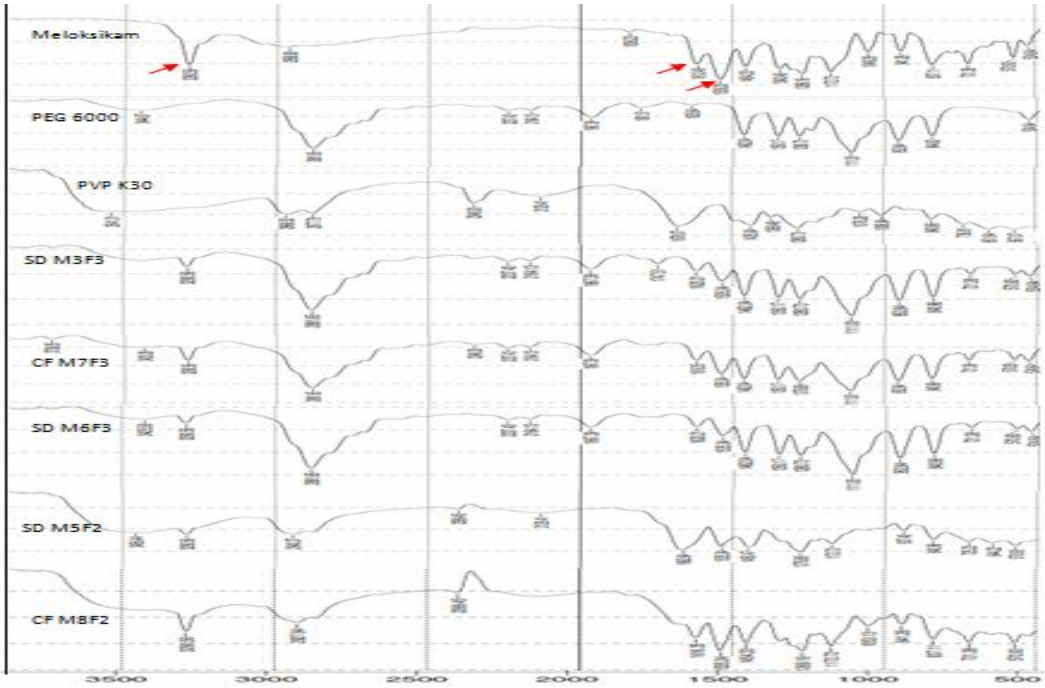

Fig 4. The infrared spectra meloxicam, PEG 6000, PVP K30, solid dispersion and physical mixture meloxicam-polymer.

Infrared absorption spectrum of substances solid dispersion and physical mixture of drug-polymer occurred a little shift in absorption band due to drug and polymer molecular bonds. As in widening the peak at 3444 cm-1 region causing overlapping OH group of PEG 6000 and NH groups of meloxicam. The same thing happened in the area in 1612 (NH), 1539 (CO) of PEG 6000 and 1678 (NH) of PVP K30. As a result, the peak of meloxicam is still visible but more gentle. It shows that the mixing of the two materials between meloxicam and polymers (PEG 6000 and PVP K30) no reaction occurs or does not occur functional group interaction chemically[1].

The results obtained from the analysis of the chemical physics meloxicam powder mixture with a polymer (PEG 6000 or PVP K30) both in solid dispersion system or physical mixture shows the interaction between meloxicam with a polymer that changes meloxicam particles of crystalline form into amorphous form. A three-dimensional crystalline form of an irregular shape, have a fixed pattern, in contrast to amorphous form. Amorphous form has irregular structure and have a higher solubility than a crystalline form so that these changes make the dissolution of meloxicam increases. The increased solubility also as a result of the wettability properties and hydrophobic polymer compound used in the formulations in solid dispersion system [11; 12].

References:

1. Retnowati, D., and Setiawan, D., Peningkatan Disolusi Ibuprofen Dengan Sistem Dispersi Padat Ibuprofen-PVP K90. Surabaya: Majalah Farmasi Airlangga., 2010, 24.
2. Chio, W.L., and Riegelman, S., Pharmaceutical Aplication of Solid Dispersion System. Journal of Pharmaceutical Science., 1971, 1282-1283; 1294-1297
3. Mogal, S.A., Gurjar, P.N., Yamgar, and Kamod, A.C., Solid Dispersion Technique For Improving of Some Poorly Soluble Drugs. Scholars Research. Der pharmacia letter., 2012, 1574
4. Corrigan, I., Mechanisms of Dissolution of Fast Release Solid Dispersion. Drug Dev. Ind. Pharm.,1985, 11.697
5. Sweetman, S.C., Martindale 36 The Complite Drug Reference. London: Pharmaceutical Press., 2009, 81, 1414
6. Salman and Erizal., Karakterisasi Fisikokimia dan Laju disolusi Dipsersi Padat Ibu Profen dengan Pembawa Polietilen Glokol 6000. Unand-Press., 2010.
7. Saharan, A.Vicas, Vippin, K., Mahesh, K., Manoj, G., and Pratim, K.C., Dissolution Enhancement of Drugs. Part. I: Technologies and Effect of Carriers. International journal of Health Risearch., 2009, 112-113.
8. Wisudyaningsih, B., Formulasi dan Uji Stabilitas Dispersi Solid Meloksikam dalam Sediaan gel. Universitas Jember-press., 2013
9. Panneerselvam, M., Natrajan, R., selvaraj, S., and Rajedran,N.N., A Novel Drug-Drug solid Dispersion Of Hydrochlorothiazide Losartan Potassium. International Journal of Pharma and Bio Sciences., 2010, 0975-6299.
10. Sutriyo, Rosmaladewi, and Filosane, F.H., Pengaruh Polivenil Pirolidon Terhadap Laju Disolusi Furosemid dalam Sistem Dispersi Padat. Depok: Majalah Ilmu Kefarmasian., 2005, 30-42.
11. Hassan. Moh. G, and Dehgan, Moh. Jafar., Improving Dissolution Meloxicam Using Solid Dispersion. Irian Journal of Pharmaceutical Research., 2006, 231-238.
12. Anwar, Z., Pengaruh Konsentrasi Polietilen Glikol (PEG) 6000 terhadap Disolusi Piroksikam dalam Dispersi Padat. Skripsi. Medan: Farmasi-USU., 2013.

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