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Research Article

SOLID SELF NANO EMULSIFYING DRUG DELIVERY SYSTEM (SOLID SNEDDS) OF MEFENAMIC ACID: FORMULA OPTIMIZATION USING AEROSIL®-200 AND AVICEL® PH-101 WITH FACTORIAL DESIGN

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ABSTRACT

Self-nanoemulsifying drug delivery system (SNEDDS) is capable of enhancing the solubility of class II BCS drugs with low solubility in water such as mefenamic acid. This system facilitates the process of solubilization to spontaneously occur in the digestive tract with little agitation. Solid SNEDDS is a form of SNEDDS solidification developed to overcome the stability problems which inhibits SNEDDS ease of use. Solid SNEDDS of mefenamic acid was performed using adsorption method on porous carriers aerosil®-200 and avicel® PH-101. Factorial design was utilized to determine the influence of carrier and proportion of carrier to liquid form of SNEEDS. The acquired solid SNEDDS retained excellent drug content yield with a value of 100.355% along with favorable good flow and compressibility properties. Morphology analysis with SEM indicates the porous carrier was capable in completely adsorbing SNEDDS on the surface while maintaining the physical form. Solid SNEDDS was able to significantly increase the dissolution of mefenamic acid which can be seen from higher percent dissolution efficiency values (43.925 ± 0.5) % compared with generic tablets (17.865 ± 0.058)% and capsules containing pure mefenamic acid (9.396 ± 0.009)%. Analysis of stability using various temperatures demonstrated the ability of solid SNEDDS to protect the content of mefenamic acid leading to better stability. Additionally, FTIR analysis did not show any interaction between the optimum formula components of solid SNEDDS. These results conclude that aerosil®-200 and avicel® PH-101 was able to act as a solid porous carrier of SNEDDS while simultaneously improving dissolution and stability.

Keywords: solid SNEDDS, mefenamic acid, avicel® PH-101, aerosil®-200, factorial design

INTRODUCTION

Self-nanoemulsifying drug delivery system (SNEDDS) is a system composed of a mixture of oils, surfactants, and co-surfactants that is able to form spontaneous nanoemulsions when in contact with the aqueous phase through mild agitation in the stomach[1]. SNEDDS can increase the solubility of drugs with low solubility in water or generally can be classified into biopharmaceutical classification system (BCS) class II or IV. Mefenamic acid which is one of the BCS class II drugs have poor solubility will lead to poor dissolution in the gastrointestinal tract leading to delayed and limited absorption and ultimately limits its clinical effectivity[2-4]. Despite its clinical importance, long term use mefenamic acid is limited due to the gastrointestinal side effect it exerted, which leads to the importance on alternative strategies to reduce the dose while maintaining similar clinical outcome[5]. Research conducted by Mardiyanto *et al.*[6] indicate conclusive results of SNEDDS comprised of capryol-90, polysorbate-80, and polyethylene glycol (PEG) 400 was able to significantly increase the dissolution of mefenamic acid compared to marketed tablets

SNEDDS have been developed into solid SNEDDS to mitigate problems of SNEDDS such as stability and ease of administration (acceptability for patients). Solid SNEDDS is a solidification of SNEDDS system by using a certain porous carrier[7-9]. By changing the physical form of SNEDDS into a dry solid system will increase the stability of the nanoemulsion system. This will expedite the robustness of future uses and handling process[8]. In this study of solidification of liquid SNEDDS was carried out by adsorption method using two types of porous carrier granules, aerosil® 200 and avicel® PH-101 along with a combination of both. Combination of both aerosil® 200 and avicel® PH-101 is expected to increase adsorption of SNEDDS and improve granule characteristics[7]. Optimization of the solid SNEDDS formula was conducted using design factorial methods three levels and two factors (3^2). Factorial design method facilitates the determination of influence from each and interaction between factors on the responses yielded[10, 11]. This method will minimize the number of trials to obtain the optimum formula of solid SNEDDS[12]. This research will delve further on the effects of solid porous carriers as potential aids to increase the efficacy and reduce side effect of mefenamic acid in therapeutical uses.

MATERIALS AND METHODS

Materials and Instruments

Mefenamic acid used in this research is a pharmaceutical grade raw material purchased from Dexa Medica, Indonesia while capryol-90 as the oil phase was a kind gift from PT Menjangan Sakti, Indonesia. Other materials used in this study were analytical and pharmaceutical grade obtained from trusted suppliers with certificate of analysis (CoA). Analytical instruments used in this study have all been calibrated and maintained under operational conditions. Scanning electron microscopy (SEM) analysis was conducted in Central Polymer Laboratory in Banten, Indonesia.

SNEDDS of Mefenamic Acid Preparation

Mefenamic acid was diluted in capryol-90 using magnetic stirrer with a speed of 150 rpm and PEG-400 was then added to the solution. In the final stage, polysorbate-80 was added and the mixture was sonicated with a bath sonicator briefly to obtain a clear yellow solution. Amount of each component follow the result of previous study conducted by Mardiyanto *et al*[6].

Solid SNEDDS Mefenamic Acid Preparation

The liquid SNEDDS formula was added dropwise onto the surface of the porous carrier with a ratio of liquid SNEDDS to porous carrieras shown in Table 1. Liquid SNEDDS was mixed with the porous carrier until adsorbed completely with no visible liquid on the surface.

Characterization of Solid SNEDDS Mefenamic Acid

Angle of Repose

Angle of repose and flow properties of solid SNEDDS were observed using the funnel method. The height of the funnel was set at 4 cm above the surface and the mass of the powder used for analysis was 10 g. The sample is carefully weighed and then flowed through the funnel. The stationary angle was calculated using Eq. 1 of flow time with an angle of repose of not more than 30°[13].

$$q = \mathrm{Tan}^{-1}\left(\frac{\text{height of powder}}{\text{radius of powder}}\right) \quad \text{(Eq. 1)}$$

Compressibility Analysis (Hausner Ratio and Carr's Index)

Solid SNEDDS granule was weighed and inserted into a cylinder tube in the volumenometer. The time and speed were set to normal. Observation was made from the initial bulk volume of the granule and after the tapping procedure was finished. Hausner ratio and Carr's index of the observed results was calculated (Eq. 2 and 3) to determine the results[13].

$$\text{Hausner Ratio} = \frac{\text{Mass of granule} / \text{Tap volume}}{\text{Mass of granule} / \text{Bulk volume}} \quad \text{(Eq. 2)}$$

$$\text{Carr's Index} = \frac{\left[\left(\text{Mass of granule} / \text{Tap volume}\right) - \left(\text{Mass of granule} / \text{Bulk volume}\right)\right]}{\text{Mass of granule} / \text{Tap volume}} \times 100\% \quad \text{(Eq. 3)}$$

Drug Content

Calibration series of concentration were created as an external standard. Mefenamic acid was diluted in methanol p.a. to create calibration solution of 80, 40, 20, 10, and 5 ppm. The determination of mefenamic acid levels in solid SNEDDS was measured using a UV-Vis spectrophotometer. Wavelength scan was conducted prior to analysis to determine the maximum wavelength of analysis.

Determination of Solid SNEDDS Mefenamic Acid Optimum Formula

The optimization was based on data of characteristic test of solid SNEDDS granules and drug content from nine formulas. The importance of each response was set according to the desired criteria. A desirability value approaching 1 indicates the best formula.

Solid SNEDDS Mefenamic Acid Morphology

The particle shape and characteristics of the optimum formula of solid SNEDDS mefenamic acid were analyzed using scanning electron microscope (SEM). Samples are placed on top of a carbon type then thinly coated with gold before inspection.

Chemical Interaction Study with FTIR

Sample powder (optimum formula solid SNEDDS of mefenamic acid and optimum formula solid SNEDDS without mefenamic acid) and dry potassium bromide marker (KBr) are mixed slowly inside the mortar which were then compacted to disc shape. Measurement was observed at wave numbers of 4000 - 400 cm^{-1}.

Dissolution Test

Dissolution test was performed by apparatus II type (paddle) with 100 rpm rotation speed in 500 mL simulated intestinal fluid (SIF) pH 7.4 with temperature 37 ± 0.5ºC. Solid SNEDDS of mefenamic acid and pure mefenamic acid powder 500 mg of mefenamic acid were inserted into a number 00 size capsules. The liquid was sampled at certain intervals, on minute 0, 5, 10, 15, 30, 45, and 60. Each 5 mL aliquot retrieval is immediately restored by 5 mL SIF into the dissolution test apparatus to maintain the sink condition. The aliquot was filtered with filter paper and its absorbance is measured by a UV-Vis spectrophotometer[1].

Thermodynamic Stability Test

The optimum formula of solid SNEDDS of mefenamic acid and pure mefenamic acid powder was put into vials, subsequently conditioned in the temperature range of 40, 50, and 60°C in the oven. The next step was to determine the concentration of each sample at each hour from the zero until the time the drug content has been reduced to 90% of initial concentration. Rate of degradation was calculated from the study to determine whether solid SNEDDS was able to increase stability.

RESULTS AND DISCUSSION

Preparation of Mefenamic Acid Solid SNEDDS

Preparation of solid SNEDDS was conducted using wet granulation method to produce a more compact granule. The purpose of this granulation process is to improve the flow properties of the porous carrier used. The granule form is more physically and chemically stable than the powder. Porous carrier is added with 2% gelatin solution as a binder in the granulation process. The binder provides adhesion to the mass of the powder during granulation[12]. Resulting organoleptic of solid SNEDDS was smooth, with no apparent discoloration and clumps.

Table 1: Preparation of Solid SNEDDS mefenamic acid

Formula	Porous Carrier	Ratio (Porous Carrier:Liquid SNEDDS)
1	Avicel® PH-101	1:1 (50%)
2	Avicel® PH-101	1:2 (67%)
3	Avicel® PH-101	1:3 (75%)
4	Aerosil® 200 - Avicel® PH-101	1:1 (50%)
5	Aerosil® 200 - Avicel® PH-101	1:2 (67%)
6	Aerosil® 200 - Avicel® PH-101	1:3 (75%)
7	Aerosil® 200	1:1 (50%)
8	Aerosil® 200	1:2 (67%)
9	Aerosil® 200	1:3 (75%)

Table 2: Flow time and angle of repose analysis

Formula	Flow Time (second)	% CV	Angle of Repose ± SD	% CV
1	Not flowing		Not flowing	
2	0.8	$1.7x10^{-14}$	13.379° ± 0.446	3.335
3	0.7	$1.9x10^{-14}$	11.746° ± 0.362	3.087
4	Not flowing		Not flowing	
5	0.9	0.00	14.808° ± 0327	2.208
6	1.2	4.95	16.775° ± 0.372	2.220
7	Not flowing		Not flowing	
8	1	0.00	13.514° ± 0.268	1.989
9	1.1	0.00	16.444° ± 0.245	1.493

Table 3: Results of Hausner ratio and Carr's index evaluation

Formula	*Bulk Density*	*Tapped Density*	Hausner Ratio	Carr's Index
1	0.500	0.588	1.176	15
2	0.556	0.588	1.059	5.556
3	0.526	0.556	1.056	5.263
4	0.556	0.588	1.059	5.556
5	0.476	0.526	1.105	9.523
6	0.454	0.476	1.047	4.545
7	0.476	0.625	1.312	23.81
8	0.416	0.434	1.043	4.167
9	0.370	0.384	1.038	3.703

Table 4: Percent recovery of mefenamic acid solid SNEDDS

Formula	Average Concentration (ppm) ± SD	% Recovery	% CV
1	7.000 ± 0.217	71.138	3.097
2	7.363 ± 0.167	112.250	2.263
3	3.906 ± 0.058	79.401	1.506
4	7.151 ± 0.221	72.677	3.093
5	6.583 ± 0.167	100.355	2.531
6	4.815 ± 0.179	97.879	3.717
7	6.636 ± 0.307	67.442	4.638
8	6.363 ± 0.227	97.006	3.577
9	4.242 ± 0.167	86.228	3.940

Table 5: Mefenamic acid pure and solid SNEDDS stability analysis results

Hour	Percentage of Mefenamic Acid in Sample					
	Temperature 40°C		Temperature 50°C		Temperature 60°C	
	Pure Mefenamic Acid	Solid SNEDDS	Pure Mefenamic Acid	Solid SNEDDS	Pure Mefenamic Acid	Solid SNEDDS
0	100	100	100	100	100	100
1	97.455	99.119	96.986	99.004	92.779	98.429
2	96.837	97.548	95.958	97.318	90.987	96.743
3	94.968	95.479	90.121	94.636	86.292	93.103
4	90.343	92.950	86.539	92.145	77.586	89.080
5	89.531	90.804	78.236	89.617	68.145	85.364

Table 6: Interpretation of FTIR spectra from samples

Possible functional groups	Theoretical wavenumber (cm^{-1})	Sample Wavenumber (cm^{-1})		
		pure mefenamic acid	optimum formula of S-SNEDDS mefenamic acid	porous carrier avicel® PH-101 - aerosil®-200
C=O	1511 – 1725	1651.07		
N-H	3200 – 3500	3309.85		
Substituted-O	893	894.97		
OH	2400 – 3500		3417.8	3410.15

Table 7: The kinetics order and release mechanism of mefenamic acid on the optimum formula of S-SNEDDS, generic tablets and pure mefenamic acid powder

Dissolution Models	Optimum Formula		Generic Tablets of Mefenamic Acid		Pure Powder of Mefenamic Acid	
	R^2	K	R^2	K	R^2	K
Zero order	0,9572	0,7217	0,6437	0,3048	0,7215	0,1563
First order	0,979	0,009	0,5591	0,023	0,5566	0,0210
Higuchi	0,8828	7,0566	0,7872	3,4315	0,8563	1,7333
Korsmeyer-Peppas	0,8073	0,194	0,869	0,6561	0,866	0,6179
Weibull	0,8077	0,6275	0,8662	43,859	0,8517	3,8955
Baker-Lonsdale	0,984	0,0561	0,6437	0,7813	0,7215	1,5238

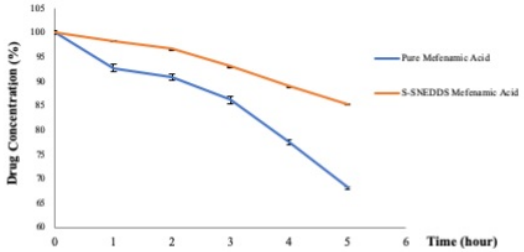

Figure 1: Reduction in mefenamic acid concentration observed at 60°C

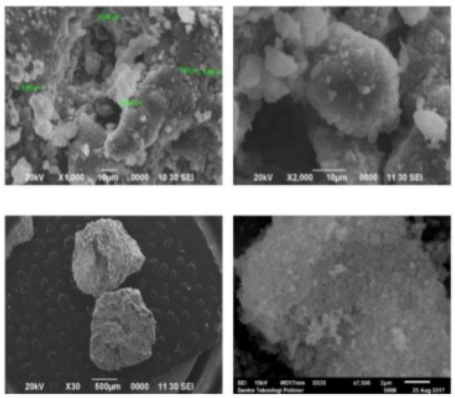

Figure 2: Morphology of optimum formula SOLID SNEDDS of mefenamic acidusing SEM (a) magnification 1000x, (b) magnification 2000x, (c) 30x magnification, (d) morphology porous carrier avicel® PH-101-aerosil®-200 magnification 7500 x

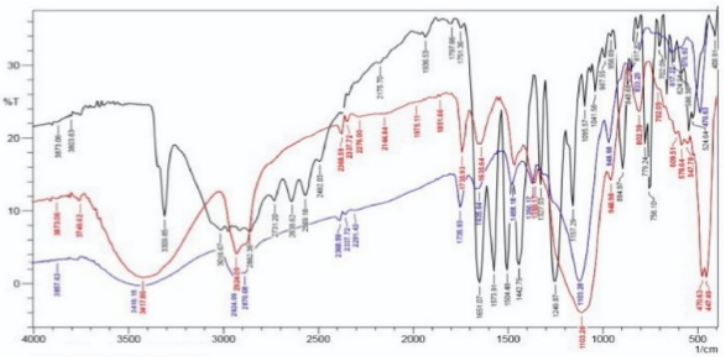

Figure 3: FTIR spectra of pure mefenamic acid, solid SNEDDS mefenamic acid of optimum formula, and porous carrier

Description:

Pure mefenamic acid

Optimum formula of solid SNEDDS mefenamic acid

Porous carrier avicel® PH-101-aerosil®-200

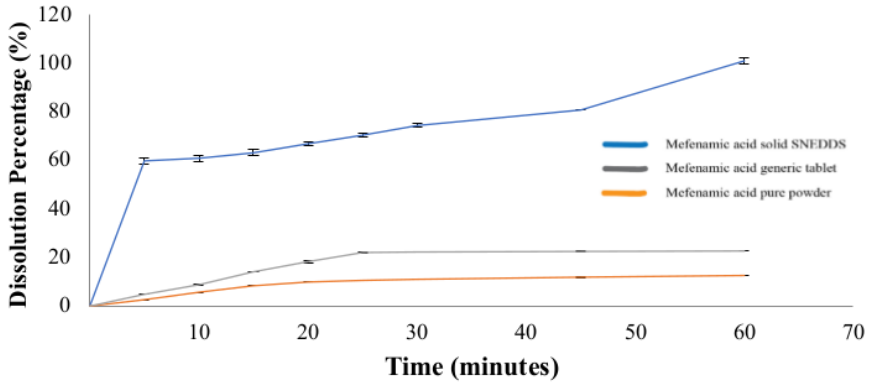

Figure 4: Percentage of dissolution comparison between solid SNEDDS, pure mefenamic acid powder form and marketed tablet

Characteristics Evaluation of Mefenamic Acid Solid SNEDDS

Flow Time and Angle of Repose

Powder flow characteristics are important in the handling of the powder and the forging process as it relates to the manufacturing process such as mixing, granulation, drying, and filling. Evaluation of each formula that successfully meets the criteria of flow time are formula 2, 3, 5, and 8 with the condition that the flow time is maximum of 10 g/second (Table 2). The faster the time it takes the mass 10 g of granules the flowing ability will get better and vice versa. Formulas 2, 3, 5, 6, 8 and 9 meet the criteria of the angle testing that have good flow properties because of the resulting alpha angle of repose below 20°[14]. Analysis of variance (ANOVA) yields different results for each factor. The porous carrier type has no significant effect on the flow time and angle of repose however ratio of porous carrier to SNEDDS influences the characteristics significantly.

Compressibility Analysis (Hausner Ratio and Carr's Index)

Other parameters used to determine flowability and granular compressibility properties are Hausner ratio and Carr's index[15]. Granules with a Hausner ratio below 1.25 and a percentage of compressibility between 5 - 10% indicate the resulting granules have good flowability. Formulas which satisfy both conditions were formula 2, 3, 4, 5, 6, 8 and 9 (Table 3). Similar to flow time and angle of repose results, porous carrier did not significantly influence the compressibility outcome. On the other hand, the ratio of porous carrier to liquid SNEDDS provide a significant influence to the results. These two findings can be explained by the increase in liquid content of the formulas with a higher ratio between porous carrier and liquid SNEDDS which leads to a higher affinity between particles due to cohesive forces and liquid bridge that was formed.

Drug Content

Determination of mefenamic acid levels in solid SNEDDS is important and necessary to ensure homogeneity of dose and effectivity of dosage forms[16]. The accuracy of an analytical method is defined as the proximity of accepted results as either a theoretical value to the value obtained from the measurement results. Accuracy is expressed as a recovery that according to ICH[17] acceptable recovery is 90 - 110%. As shown in Table 4, formulas 5, 6, and 8 fulfilled the criteria and can maintain homogenous content of mefenamic acid. Combination of avicel® PH-101 and aerosil®-200 that were used was efficient in adsorbing the liquid and maintaining the homogeneity of the formulation.

Determination of Optimum Formula Solid SNEDDS Mefenamic Acid

The optimum formula of solid SNEEDS of mefenamic acid was determined using Design Expert®10 based on the results of Hausner ratio, Carr's index, flow time, angle of repose, and drug content. The optimum formula was then determined by the desirability value, the closest to 1 indicates the best formula which was obtained by formula 5 with a value of 0.712. The optimum formula of solid SNEDDS of mefenamic acid was formulated into 3 batches to ensure the consistency of the resulting preparation. Further evaluations were carried out to the optimum formula.

Thermodynamic Stability

Stability testing on levels in solid SNEDDS compared with the stability of pure active substances to see the effect of dosage form on mefenamic acid stability[18,19]. The results of thermodynamic stability tests show that the dosage form of solid SNEDDS of mefenamic acid has better stability than pure mefenamic acid. Solid SNEDDS of mefenamic acid and pure mefenamic acid were estimated to have a shelf life of 13.602 hours and 0.579 hours with a half-life of 89.775 hours and 3.823 hours, respectively. Mefenamic acid is a drug that is susceptible to light and moisture. Storage of mefenamic acid at hot temperatures, high air humidity and exposure to light can damage the quality of the drug[20]. Figure 1 displays a faster rate of reduction in pure substance of mefenamic acid compared with solid SNEDDS of mefenamic acid. The solid SNEDDS dosage form was able to significantly reduce and slow the degradation of mefenamic acid due to the protection of the active ingredient by porous carrier granules.

Solid SNEDDS Mefenamic Acid Morphology

Scanning electron microscope (SEM) is a method to observe the optimum morphology of solid SNEDDS of mefenamic acid such as particle size, porosity, and surface appearance of the particle[8]. Figure 2 is the result of SEM analysis clearly displaying the surface morphology of solid SNEDDS with porous carrier. The presence of these pores supports the carrier function in adsorbing liquid SNEDDS and allowing the drug to diffuse through from its

matrix. Based on the figure there is no visible oily globule remaining on the surface of the granule compared to the porous carrier, so it is concluded that the porous carrier of avicel® PH-101 mixture with aerosil®-200 used is able to adsorb liquid SNEDDS of mefenamic acid. This is consistent with that mentioned by Patel *et al*[21] that the absence of oil globules on the surface of the solid SNEDDS granule indicates a perfect adsorption by the porous carrier employed.

Chemical Interaction Study with FTIR

FTIR analysis aims to determine the possibility of a new chemical bond in the preparation of solid SNEDDS of mefenamic acid. The new bond possibility is formed due to the interaction between porous carrier, active substance, and other additives. FTIR test results are performed by identifying the wave numbers in the IR spectra. Chemical interaction occurs when there is a new functional group formed by the interaction between pure substance of mefenamic acid with porous carrier and other additives.

Figure 3 is an IR spectrum of pure mefenamic acid, the optimum formula of solid SNEDDS of mefenamic acid and porous carrier. There is a difference between pure mefenamic acid spectra and the optimum formula of Solid SNEDDS of mefenamic acid in the form of loss of peak of mefenamic acid. This is due to the overlap of the mefenamic acid peak with a porous carrier mixture of avicel® PH-101 with aerosil®-200[8]. The spectra of solid SNEDDS of mefenamic acid in the region of wavelength number of 3500 - 3300 cm^{-1} shows the peak due to vibration of the hydrogen atom with other atoms. The peak is due to the vibration of the hydrogen atom with the oxygen atom[22]. The pure mefenamic acid spectra of the smaller ends of the band was due to the greater non-polar end of the molecule which can overlap with hydrogen bond[16]. There is no new interaction found in the spectra indicating compatibility between SNEDDS and porous carrier.

***In Vitro* Dissolution**

Dissolution tests were performed to determine the process of release of mefenamic acid from the preparation of solid SNEDDS of mefenamic acid, generic tablets and pure mefenamic acid capsules. The dissolution profile graph (Figure 4) showed solid SNEDDS mefenamic acid was able to improve the dissolution of mefenamic acid in the gastrointestinal tract significantly. The drug release profile following the first order kinetics has a drug release rate that depends on the concentration of the drug, the higher the concentration of the active substance correlates linearly with the amount of drug released. This first order kinetic profile, for example, can be found in pharmaceutical forms containing drugs in porous matrices[23]. Solid SNEDDS of mefenamic acid is a dosage form containing mefenamic acid in a spherical matrix. The Baker-Lonsdale model illustrates the mechanism of the release of mefenamic acid in a spherical matrix (porous carrier granule). The Korsmeyer-Peppas equation must be considered the value of n (release exponent) which describes the release mechanism for tablets with a cylindrical matrix, if the value of $n < 0.43$ the release of the active substance follows the Fickian diffusion mechanism. The value of n is in the range of $0.43 < n < 0.85$ indicating the release of the active substance following non-Fickian diffusion, whereas for the value of $n > 0.85$ indicates the release of the active substance following the mechanism of case II transport[24].

Generic tablets and pure substances of mefenamic acid have a drug release profile that follows the zero order. The drug release occurs slowly on the release profile following the zero order. According to Costa and Lobo[25,26], if the rate of release of mefenamic acid capsules and tablets follows the zero order, the release of mefenamic acid occurs slowly and is not affected by the concentration of mefenamic acid but the solubility of mefenamic acid to the dissolution medium. This phenomenon can be observed in this case due to mefenamic acid poor solubility in the SIF medium. The value of the release exponent produced in the dissolution of the mefenamic acid tablet is 0.6561 so that based on the Korsmeyer-Peppas model the release mechanism follows the non-Fickian diffusion which is the rate of polymer diffusion and erosion running in balance. Mechanism of release of the mefenamic acid tablets initially is erosion caused by penetration of the dissolution medium into the pores of the matrix. The diffusion mechanism is due to the insufficient medium to develop the matrix component so that the release of mefenamic acid in it occurs by diffusion.

Normality test results show that the data is normally distributed with a significance value greater than 0.05 ($p > 0.05$). Statistical analysis was then continued with one-way ANOVA test to compare percentage of dissolution efficiency (%DE) from solid SNEDDS of mefenamic acid, pure mefenamic acid and mefenamic acid generic tablets. Based on the results of the analysis yielded a significance value of less than 0.05 ($p<0.05$). It shows that the three preparations have significant differences with %DE value of solid SNEDDS of mefenamic acid, pure mefenamic acid, and mefenamic acid generic tablets were 43.924%, 9.423%, and 17.865% respectively. Based on the greater %DE value for solid SNEDDS of mefenamic acid it can be concluded that solid self-nanoemulsifying dosage form is capable of improving the dissolution process of mefenamic acid.

CONCLUSION

Porous carrier composed from a mixture of avicel® PH-101 and aerosil®200 produced favorable granules with the ability to increase dissolution and stability of mefenamic acid. The ratio between porous carrier to liquid SNEDDS affects the characteristics of the granules more significantly compared to the type of porous carrier. Resulting solid SNEDDS was able to adsorb the liquid SNEDDS fully into the carrier, creating exceptional granules which can be developed further. FTIR spectral analysis results showed between mefenamic acid and porous carrier did not display formation of new functional groups indicating there was no interaction between the drug and the carrier.

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Solid Self Nanoemulsifying Drug Delivery System (SOLID SNEDDS) of Mefenamic Acid: Formula Optimization Using Aerosil®-200 and Avicel® PH-101 with Factorial Design

Comment [p2]: Program ?

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ABSTRACT

Comment [p3]: more 300 words

Self-nanoemulsifying drug delivery system (SNEDDS) is capable of enhancing the solubility of class II BCS drugs with low solubility in water such as mefenamic acid. This system facilitates the process of solubilization to spontaneously occur in the digestive tract with little agitation. Solid SNEDDS is a form of SNEDDS solidification developed to overcome the stability problems that still exist in SNEDDSand to improve its ease of use. Solidification SNEDDS of mefenamic acid was performed using adsorption method on porous carriersaerosil®-200 and avicel® PH-101. In order to determine the influence of carrier and proportion of carrier to liquid form of SNEEDS, factorial design analysis was implemented. From the analysis results, granules characteristics of the optimum formula was favorable with good flow and compressibility properties. The mefenamic acid content of the optimum formula yields a value of 100.355% which meet the requirement. Morphology analysis with SEM indicates the porous carrier was capable in fully adsorbing SNEDDS on the surface while maintaining its physical form. FTIR analysis did not show any interaction bepolysorbate the components of the optimum formula of solid SNEDDS of mefenamic acid with the excipients. Solid SNEDDS was able to significantly increase the dissolution of mefenamic acid which can be seen from higher % dissolution efficiency values (43.925 ± 0.5)% compared with generic tablets (17.865 ± 0.058)% and capsules containing pure mefenamic acid (9.396 ± 0.009)%. Analysis of stability using various temperature showed that solid SNEDDS was able to protect the content of mefenamic acid, leading to better stability. These results conclude that aerosil®-200 and avicel® PH-101 was able to act as a solid porous carrier of SNEDDS while simultaneously improving dissolution and stability.

Keyword(s): solid SNEDDS, mefenamic acid, avicel® PH-101, aerosil®-200, factorial design

INTRODUCTION

Self-NanoemulsifyingDrug Delivery System (SNEDDS) is a system composed of a mixture of oils, surfactants, and co-surfactants that is able to form spontaneous nanoemulsions when in contact with the aqueous phase through mild agitation in the stomach. SNEDDS can increase the solubility of drugs with low solubility in water or generally can be classified into biopharmaceutical classification system (BCS) class II or IV. Mefenamic acidwhichis one of the BCS class II drugs have poor solubility will lead to poor dissolution in the gastrointestinal tract leading to delayed and limited absorption and ultimately limits its

clinical effectivity(Gupta et al., 2011). Research conducted by Mardiyanto et al. (2018) indicate conclusive results of SNEDDS comprised of capryol-90, polysorbate-80, and PEG-400 was able to significantly increase the dissolution of mefenamic acid compared to marketed tablets.

SNEDDS have been developed into SOLID SNEDDS (Solid Self-Nanoemulsifying Drug Delivery System) to mitigate problems of SNEDDS such as stability and ease of administration (acceptability for patients). Solid SNEDDS is a solidification of SNEDDS system by using a certain porous carrier. By changing the form of SNEDDS into a dry solid system will increase the stability of the nanoemulsion system.This will facilitate the robustness of future uses and handling process. In this study of solidification of LIQUID SNEDDS was carried out by adsorption method using two types of porous carrier granules, aerosil® 200 and avicel® PH-101 and a combination of both. Combination of both aerosil® 200 and avicel® PH-101 is expected to increase adsorption of SNEDDS and improve granule characteristics. Optimization of the SOLID SNEDDS formula using design factorial methods three levels and two factors (3^2). Factorial design method allows to identify the effect of each factors and interaction between factors on the response in the form of powder properties and drug content. This method will minimize the number of trials to obtain the optimum formula SOLID SNEDDS

Comment [p4]: solid SNEDDS investigation ?

Comment [p5]: explain in the method

MATERIALS AND METHODS

Materials and equipments

Mefenamic acid used in this research is a pharmaceutical grade raw material purchased from DexaMedica. Capryol-90 used as the oil phase was a kind gift from PT Menjangan Sakti, Indonesia. Other materials used in this study are analytical and pharmaceutical grade obtained from trusted suppliers. Analytical instruments used in this study have all been calibrated and maintained under operational conditions. Scanning electron microscopy (SEM) analysis was conducted in Central Polymer Laboratory in Banten, Indonesia.

SNEDDS ofMefenamicAcidPreparation

Mefenamic acid was diluted in capryol-90 using magnetic stirrer with a speed of 150 rpm and PEG-400 was then added to the solution In the final stages, polysorbate-80 was added and the mixture was sonicated with a bath sonicator briefly to obtain a clear yellow solution. Amount of each component follow the result of previous study conducted by Mardiyanto et al. (2018).

Solid SNEDDS Mefenamic Acid Preparation

The liquid SNEDDS formula was poured slowly onto the surface of the porous carrier with a ratio of liquid SNEDDS to porous carrieras shown in Table 1. Mix until liquid SNEDDS is completely absorbed until a good mixture is formed.

Characteristics Test of Solid SNEDDSMefenamic Acid

Angle of Repose

Angle of repose and flow properties of solid SNEDDSwas observed using the funnel method. The height of the funnel was set at 4 cm above the surface and the mass of the powder used is 10 g. The sample is carefully weighed and then flowed through the funnel. The stationary angle was calculated using Eq 1 of flow time with an angle of repose of not more than 30°.

Compressibility Analysis (Hausner Ratio and Carr's Index)

Solid SNEDDS granule was weighed and inserted into a cylinder tube in the volumenometer. The time and speed were set to normal. Observe the initial bulk volume of the granule and after the tapping procedure was finished. Calculate the Hausner ratio and Carr's Index of the observed results.

Drug Content

Calibration series of concentration were created as an external standard. Mefenamic acid was diluted in methanol p.a. to create calibration solution of 80, 40, 20, 10, and 5 ppm. The determination of mefenamic acid levels in solid SNEDDS was measured using a UV-Vis

spectrophotometer. Wavelength scan was conducted prior to analysis to determine the maximum wavelength of analysis.

Determination of Solid SNEDDS Mefenamic Acid Optimum Formula

The optimization was based on data of characteristic test of solid SNEDDS granules and drug content from nine formulas. The importance of each response is set according to the desired criteria. A desirability value approaching 1 indicates the best formula.

Solid SNEDDS MefenamicAcidMorphology

The particle shape and characteristics of the optimum formula of solid SNEDDS mefenamic acid were analyzed using scanning electron microscope (SEM). Samples are placed on top of a carbon type then thinly coated with gold before inspection.

ChemicalInteractionStudy WithFTIR

Sample powder (optimum formula solid SNEDDS of mefenamic acid and optimum formula solid SNEDDS without mefenamic acid) and dry potassium bromide marker (KBr) are mixed slowly inside the mortar, compacted to disc shape. Measurement was observed at wave numbers of 4000 - 400 cm^{-1}.

Dissolution Test

Dissolution test was performed by apparatus II type (paddle) with 100 rpm rotation speed in 500 mL simulated intestinal fluid (SIF) pH 7.4 with temperature 37 ± 0,5ºC. SOLID SNEDDS of mefenamic acid and pure mefenamic acid powder 500 mg of mefenamic acid were inserted into a number 00 capsules. The liquid was sampled at certain intervals, on minute 0, 5, 10, 15, 30, 45, and 60. Each 5 mL aliquot retrieval is immediately restored by 5 mL SIF into the dissolution test apparatus to maintain the sink condition. The aliquot was filtered with filter paper and its absorbance is measured by a UV-Vis spectrophotometer.

Thermodynamic Stability Test

The optimum formula of solid SNEDDS of mefenamic acid and pure mefenamic acid powder was put into vials, subsequently conditioned in the temperature range of 40, 50, and 60° C in the oven. The next step was to determine the concentration of each sample at each hour from the zero until the time the drug content has been reduced to 90% of initial concentration. Rate of degradation was calculated from the study to determine whether solid SNEDDS was able to increase stability.

RESULTS AND DISCUSSION

Preparation of Mefenamic Acid Solid SNEDDS

Preparation of solid SNEDDS was conducted using wet granulation method to produce a more compact granule. The purpose of this granulation process is to improve the flow properties of the porous carrier used. The granule form is more physically and chemically stable than the powder. Porous carrier is added with 2% gelatin solution as a binder in the granulation process. The binder provides adhesion to the mass of the powder during granulation. Resulting organoleptic of solid SNEDDS was smooth, with no apparent discoloration and

Characteristics Evaluation of Mefenamic Acid Solid SNEDDS

Flow Time and Angle of Repose

Powder flow characteristics are important in the handling of the powder and the forging process as it relates to the manufacturing process such as mixing, granulation, drying, and filling. Evaluation of each formula that successfully meets the criteria of flow time areformula 2, 3, 5, and 8 with the condition that the flow time is maximum of 10 g/second. The faster the time it takes the mass 10 g of granules the flowing ability will get better and vice versa. Formulas 2, 3, 5, 6, 8, and 9 meet the criteria of the angle testing that have good flow properties because of the resulting alpha angle of repose below 20^{o} (Gandhi, 2012). Result of this analysis can be viewed in Table 2.Analysis of variance (ANOVA) yields different results for each factor. The porous carrier type has no significant effect on the flow time and angle of repose however ratio of porous carrier to SNEDDS influence the characteristics significantly.

Compressibility Analysis (Hausner Ratio and Carr's Index)

Other parameters used to determine flowability and granular compressibility properties are Hausner ratio and Carr's index(Ngwuluka et al., 2010). Granules with a Hausner ratio below 1.25 and a percentage of compressibility between 5 - 10% indicate that granules have good flowability (Bodhmage, 2006). Formulas that satisfy both conditions are formula 2, 3, 4, 5, 6, 8, and 9 (Table 3).

Drug Content

Determination of mefenamic acid levels in solid SNEDDS is important and necessary to ensure homogeneity of dose and effectivity of dosage forms(Abraham et al. 2012). The accuracy of an analytical method is defined as the proximity of accepted results as either a theoretical value to the value obtained from the measurement results. Accuracy is expressed as a recovery that according to ICH (2005) acceptable recovery is 90 - 110%.

Determination of Optimum FormulaSolid SNEDDS Mefenamic Acid

The optimum formula of S-SNEEDS of mefenamic acid was determined using Design Expert®10 regulated by Hausner's ratio criteria,% CV uniformity size, minimum flow and rest time, while Carr in range index and targeted drug content. The importance of the drug content is adjusted to level 5 indicating that the drug content in the preparation is the main requirement of the optimum formulation. The greater the importance value signifies that these criteria become very important. Determination of optimum formula based on the desirability value that closest to 1 is the formula 5 which has a desirability value of 0.712.

The optimum formula of SOLID SNEDDS of mefenamic acid is made into 3 batches to know and ensure the consistency of the resulting preparation has the same quality. Further evaluations were carried out as was done to obtain the optimum formula for the 3 batches. The determination of the flow profile carried out through the flow time and the fixed angle of the optimum formula yields the average value and% of the eligible CV, as well as the Hausner and Carr indices. The three batches of the optimum SOLID SNEDDS mefenamic acid generated formula have good sized uniformity seen through the% CV values of each adjacent batch. Each batch of optimum formula of SOLID SNEDDS of mefenamic acid also meets the grade requirement because it is in the range 90 - 110% with% CV below 5%.

Thermodinamic Stability

Stability testing on levels in SOLID SNEDDS compared with the stability of pure active substances to see the effect of dosage form on mefenamic acid stability (WHO, 1997).The results of thermodynamic stability tests show that the dosage form of solid SNEDDS of mefenamic acid has better stability than pure mefenamic acid. Solid SNEDDS of mefenamic acid and pure mefenamic acid were estimated to have a shelf life of 13.602 hours and 0.579 hours with a half-life of 89.775 hours and 3.823 hours, respectively. Mefenamic acid is a drug that is susceptible to light and moisture. Storage of mefenamic acid at hot temperatures, high air humidity, and exposure to light can damage the quality of the drug. Figure 1 shows a faster rate of reduction in pure substance of mefenamic acid compared with solid SNEDDS of mefenamic acid. The solid SNEDDS dosage form is able to slow the degradation of mefenamic acid because the active ingredient is protected by porous carrier granules.

Solid SNEDDS Mefenamic Acid Morphology

Scanning electron microscope (SEM) is a method to observe the optimum morphology of solid SNEDDS of mefenamic acid such as particle size, porosity, and surface appearance of the particle. Figure 2 is the result of SEM analysis showing clearly the surface morphology of solid SNEDDS with porous carrier. The presence of these pores supports the carrier function in adsorbing liquid SNEDDS and allowing the drug to diffuse through from its matrix.Based on the figure there is no visible oily globule remaining on the surface of the granule compared to the porous carrier so it is concluded that the porous carrier of avicel® PH-101 mixture with aerosil®-200 used is able to adsorb liquid SNEDDS of mefenamic acid. This is consistent with that mentioned by Patel (2014) that the absence of oil globules on the surface of the solid SNEDDS granule indicates a perfect adsorption by the porous carrier employed.

Chemical Interaction Study withFTIR

FTIR analysis aims to determine the possibility of a new chemical bond in the preparation of solid SNEDDS of mefenamic acid. The new bond possibility is formed due to the interaction between porous carrier, active substance, and other additives. FTIR test results are performed by identifying the wave numbers in the IR spectra. Chemical interaction occurs when there is a new functional group formed by the interaction between pure substance of mefenamic acid with porous carrier and other additives.

Figure 3 is an IR spectrum of pure mefenamic acid, the optimum formula of SOLID SNEDDS of mefenamic acid, and porous carrier. There is a difference between pure mefenamic acid spectra and the optimum formula of SOLID SNEDDS of mefenamic acid in the form of loss of peak of mefenamic acid. This is due to the overlap of the mefenamic acid peak with a porous carrier mixture of avicel® PH-101 with aerosil®-200 (Inugala, 2015). The spectra of solid SNEDDS of mefenamic acid in the region of wavelength number of 3500 - 3300 cm-1 shows the peak due to vibration of the hydrogen atom with other atoms. The peak is due to the vibration of the hydrogen atom with the oxygen atom. The pure mefenamic acid spectra of the smaller ends of the band was due to the greater non polar end of the molecule which can overlap with hydrogen bond. There is no new interaction found in the spectra indicating compatibility between SNEDDS and porous carrier.

In Vitro Dissolution

Dissolution tests were performed to determine the process of release of mefenamic acid from the preparation of solid SNEDDS of mefenamic acid, generic tablets, and pure mefenamic acid capsules. The dissolution profile graph (Figure 4) show solid SNEDDS mefenamic acid is able to improve the dissolution of mefenamic acid in the gastrointestinal tract. The drug release profile following the first order kinetics has a drug release rate that depends on the concentration of the drug in it. The higher the concentration of the active substance the greater the amount of drug released. This one-order kinetic profile, for example, can be found in pharmaceutical forms containing drugs in porous matrices (Mulye and Turco, 1995). solid SNEDDS of mefenamic acid is a dosage form containing mefenamic acid in a spherical matrix. The Baker-Lonsdale model illustrates the mechanism of the release of mefenamic acid in a spherical matrix (porous carrier granule).The Korsmeyer-Peppas equation must be considered the value of n (release exponent) which describes the release mechanism. For tablets with a cylindrical matrix, if the value of n <0.43 the release of the active substance follows the Fickian diffusion mechanism. The value of n is in the range of 0.43 <n <0.85 indicating the release of the active substance following non-Fickian diffusion, whereas for the value of n> 0.85 indicates the release of the active substance following the mechanism of case II transport (Siepmann and Peppas, 2001).

Comment [p6]: why liquid to solid did not change the diffusion pattern ?

Generic tablets and pure substances of mefenamic acid have a drug release profile thatfollows the zero order. The drug release occurs slowly on the release profile following the zero order. According to Costa and Lobo (2001), if the rate of release of mefenamic acid capsules and tablets follows the zero order, the release of mefenamic acid occurs slowly and is not affected by the concentration of mefenamic acid but the solubility of mefenamic acid to the dissolution medium. This is because the mefenamic acid has a poor solubility in the SIF medium.The value of the release exponent produced in the dissolution of the mefenamic acid tablet is 0.6561 so that based on the Korsmeyer-Peppas model the release mechanism follows the non-Fickian diffusion ie the rate of polymer diffusion and erosion running in balance The mechanism of release of the mefenamic acid tablets initially is erosion caused by penetration of the dissolution medium into the pores of the matrix. The diffusion

mechanism is due to the insufficient medium to develop the matrix component so that the release of mefenamic acid in it occurs by diffusion.

Normality test results show that the data is normally distributed with a significance value greater than 0.05 (α). One way ANOVA test was used to compare% DE from SOLID SNEDDS of mefenamic acid, pure mefenamic acid, and mefenamic acid generic tablets. Based on the results of the analysis yielded a significance value of less than 0.05 (α). It shows that the three preparations have significant differences. The% DE value of SOLID SNEDDS of mefenamic acid, pure mefenamic acid, and mefenamic acid generic tablets were 43.924%, 9.423%, and 17.865%, respectively. Based on the greater% DE value for solid SNEDDS of mefenamic acid it can be concluded that the solid self-nanoemulsifying dosage form is capable of improving the dissolution process of mefenamic acid.

CONCLUSIONS

Comment [p7]: high light the intended application

Porous carrier composed of a mixture betwenavicel® PH-101-aerosil®200 produces good favorable granules with the ability to increase dissolution and stability of mefenamic acid. Resulting solid SNEDDS was able to adsorb the liquid SNEDDS fully into the carrier, creating good granules which can be developed further. FTIR spectral analysis results showed between mefenamic acid and porous carrier did not show the formation of new functional groups indicating there is no interaction.

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Comment [p8]: see instruction

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List of Tables

Table 1. Preparation of SOLID SNEDDS mefenamic acid

Liquid SNEDDS	***Porous carrier***	**Ratio**
	Avicel® PH-101	1 : 1 (50%)
Liquid SNEDDS	Avicel® PH-101	1 : 2 (67%)
	Avicel® PH-101	1 : 3 (75%)
	Aerosil® 200 - Avicel® PH-101	1 : 1 (50%)
Liquid SNEDDS	Aerosil® 200 - Avicel® PH-101	1 : 2 (67%)
	Aerosil® 200 - Avicel® PH-101	1 : 3 (75%)
	Aerosil® 200	1 : 1 (50%)
Liquid SNEDDS	Aerosil® 200	1 : 2 (67%)
	Aerosil® 200	1 : 3 (75%)

Table 2. Flow time and angle of repose analysis

Formula	**Flow Time (second)**	**% CV**	**Angle of Repose ± SD**	**% CV**
1	Not flowing		Not flowing	
2	0.8	$1.7x10^{-14}$	$13.379^{o} \pm 0.446$	3.335
3	0.7	$1.9x10^{-14}$	$11.746^{o} \pm 0.362$	3.087
4	Not flowing		Not flowing	
5	0.9	0,00	$14.808^{o} \pm 0327$	2.208
6	1.2	4,948	$16.775^{o} \pm 0.372$	2.220
7	Not flowing		Not flowing	
8	1	0,00	$13.514^{o} \pm 0.268$	1.989
9	1.1	0,00	$16.444^{o} \pm 0.245$	1.493

Table 3. Resultsof Hausner ratioand Carr's index evaluation

Formula	***Bulk Density***	***Tapped Density***	**Hausner Ratio**	**Carr's Index**
1	0,500	0,588	1,176	15
2	0,556	0,588	1,059	5,556
3	0,526	0,556	1,056	5,263
4	0,556	0,588	1,059	5,556

5	0,476	0,526	1,105	9,523
6	0,454	0,476	1,047	4,545
7	0,476	0,625	1,312	23,81
8	0,416	0,434	1,043	4,167
9	0,370	0,384	1,038	3,703

Table 4. Percent recovery of mefenamic acid solid SNEDDS

Formula	Average Concentration (ppm) ± SD	%Recovery	% CV
1	7.000 ± 0.217	71.138	3.097
2	7.363 ± 0.167	112.250	2.263
3	3.906 ± 0.058	79.401	1.506
4	7.151 ± 0.221	72.677	3.093
5	6.583 ± 0.167	100.355	2.531
6	4.815 ± 0.179	97.879	3.717
7	6.636 ± 0.307	67.442	4.638
8	6.363 ± 0.227	97.006	3.577
9	4.242 ± 0.167	86.228	3.940

Tabel 5. Mefenamic acid pure and solid SNEDDS stability analysis results

Hour	Percentage of Mefenamic Acid in Sample					
	Temperature 40°C		Temperature 50°C		Temperature 60 °C	
	Pure Mefenamic Acid	SolidSNEDDS	Pure Mefenamic Acid	SolidSNEDDS	Pure Mefenamic Acid	SolidSNEDDS
0	100	100	100	100	100	100
1	97.455	99.119	96.986	99.004	92.779	98.429
2	96.837	97.548	95.958	97.318	90.987	96.743
3	94.968	95.479	90.121	94.636	86.292	93.103
4	90.343	92.950	86.539	92.145	77.586	89.080
5	89.531	90.804	78.236	89.617	68.145	85.364

Table 6. Interpretation of FTIR spectra from samples

Possible Functional Groups	Theoretical Wave number (cm^{-1})	Sample Wavenumber (cm^{-1})		
		pure mefenamic acid	optimum formula of S-SNEDDS mefenamic acid	porous carrier avicel® PH-101 - aerosil®-200
C=O	1511 – 1725	1651.07		
N-H	3200 – 3500	3309.85		
Substituted-O	893	894.97		
OH	2400 – 3500		3417.8	3410.15

Table 7. The kinetics order and release mechanism of mefenamic acid on the optimum formula of S-SNEDDS, generic tablets, and pure mefenamic acid powder

Dissolution Models	Optimum Formula		Generik Tablets of Mefenamic Acid		Pure Powder of Mefenamic Acid	
	R^2	K	R^2	K	R^2	K
Orde 0	0,9572	0,7217	0,6437	0,3048	0,7215	0,1563
Orde 1	0,979	0,009	0,5591	0,023	0,5566	0,0210

Higuchi	0,8828	7,0566	0,7872	3,4315	0,8563	1,7333
Korsmeyer-Peppas	0,8073	0,194	0,869	0,6561	0,866	0,6179
Weibull	0,8077	0,6275	0,8662	43,859	0,8517	3,8955
Baker-Lonsdale	0,984	0,0561	0,6437	0,7813	0,7215	1,5238

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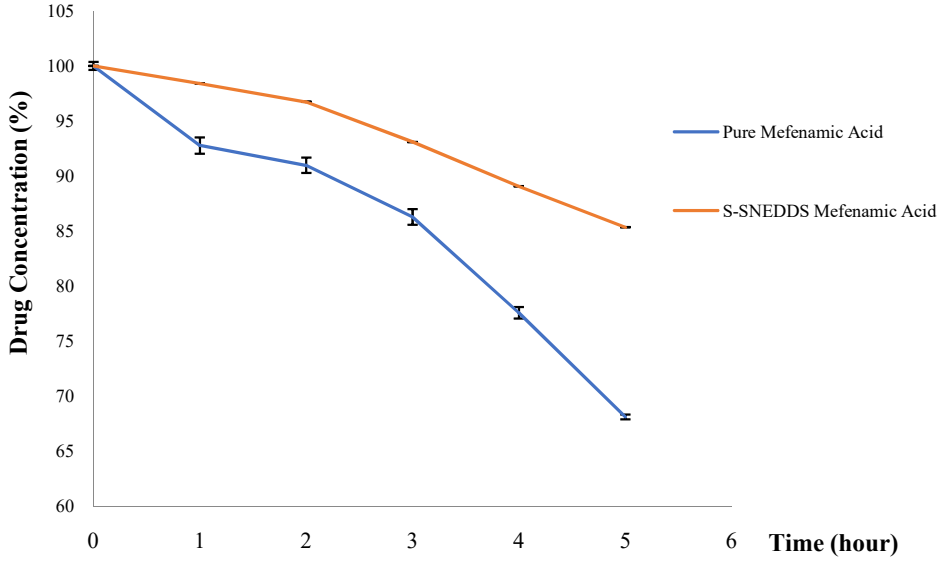

Figure 1. Reduction in mefenamic acid concentration observed at temperature 60^{o}C

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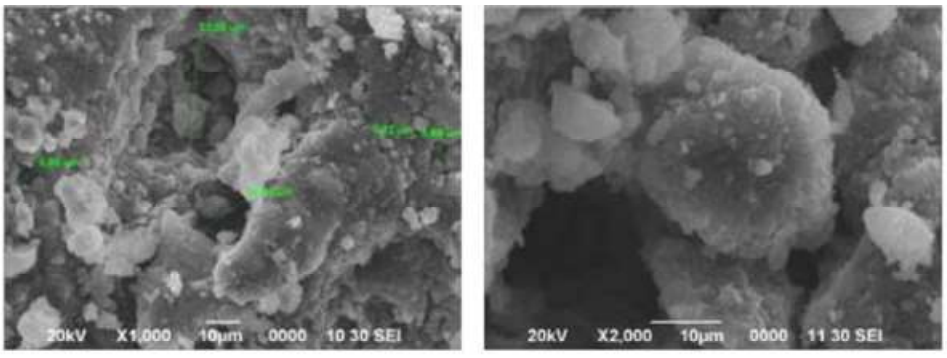

(a) **(b)**

Figure 2. Morphology of optimum formula SOLID SNEDDS of mefenamic acidusing SEM (a) magnification 1000x, (b) magnification 2000x, (c) 30x magnification, (d) morphology porouscarrier avicel® PH-101-aerosil®-200 magnification 7500 x

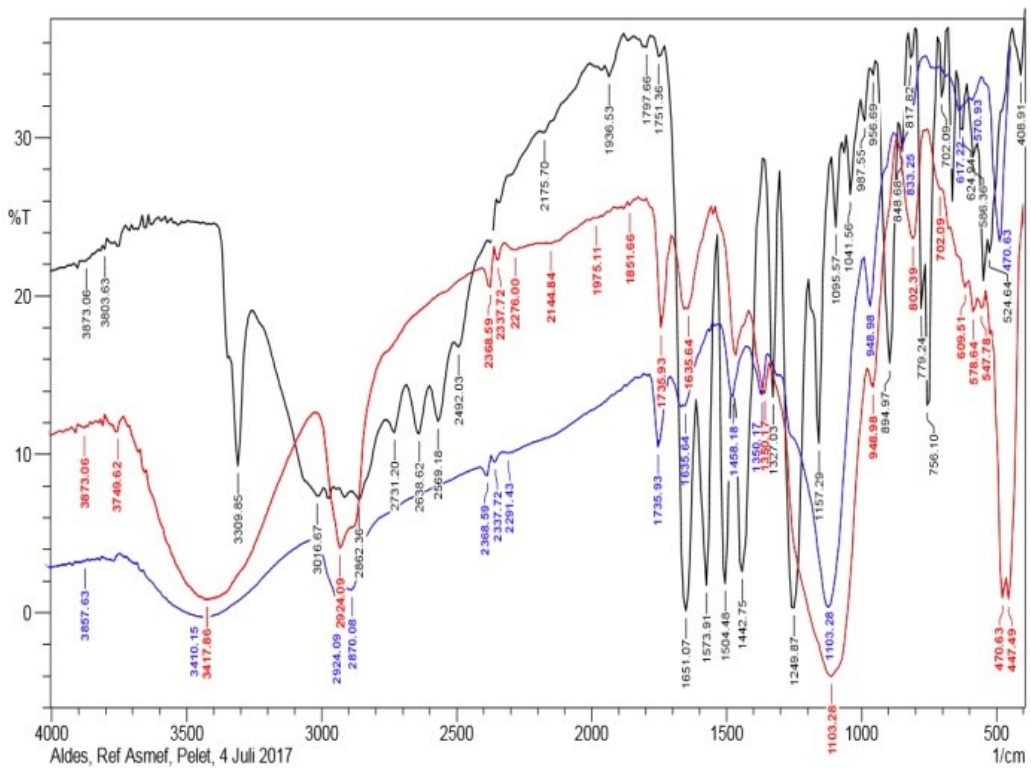

Figure 3.FTIR spectra of pure mefenamic acid, solid SNEDDS mefenamic acid of optimum formula, and porous carrier

Descriptions :

Pure mefenamic acid

Optimum formula solid SNEDDS mefenamic acid

Porous carrier avicel® PH-101-aerosil®-200

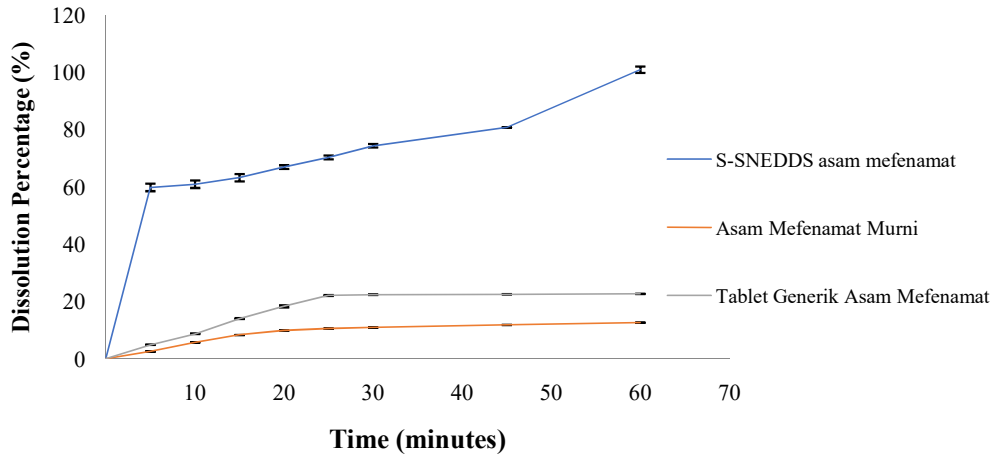

Figure 4. Percentage of dissolution between solid SNEDDS, pure mefenamic acid powder form and marketed tablet

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