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Formulation of Polyethylene Glycol Based Ibuprofen Nanosuppository Preparations and Assesment of Dissolution

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ABSTRACT

Ibuprofen is widely formulated in oral and rectal dosage forms. Ibuprofen in the rectal route shows c max and t max longer than syrup preparations, this is due to the low solubility of ibuprofen. Nanoparticles are one of the technologies that are widely used to increase the solubility of an active substance. Nanoscale particle size, can increase the solubility of ibuprofen and allow dose reduction. This study aims to formulate ibuprofen nanosuppository preparations, and test the percent dissolution of nanosuppositories compared to conventional suppositories. The ibuprofen nanosuppository formulation consists of ibuprofen lipid component and PEG mix component (PEG 4000: PEG 6000). The ibuprofen lipid component consisted of ibuprofen VCO oil, tween 80 and propylenglycol. This lipid component was then tested for physical characteristics, transmittance, particle size and zeta potential, then the lipid was added to the suppository base component. The responses observed were disintegration time, hardness, and non-intrinsic dissolution efficiency. The test results showed transmittance values of 91.98%, 92.99%, 93.26%. Particle size and potential zeta values of FI = 107, 5 nm, FII 102 nm and FIII 103 nm. The zeta potential were -16.19 mV, -12.44 and -13.25 mV in the lipid component. The test results of the disintegration time of F1, F2, F3 nanosuppositories were 12 minutes, 11 minutes and 10 minutes. The hardness of F1, F2, and F3 were 1.53 kg, 1.43 kg and 1.26 kg and the dissolution efficiency value was higher than conventional suppositories. Modification of ibuprofen nanosuppositories had a significant effect on the percent dissolution of ibuprofen.

Keyword: Nosuppositoria, Ibuprofen, Dissolution Test

ABSTRAK

Ibuprofen banyak diformulasikan dalam bentuk sediaan oral maupun rektal. Ibuprofen dalam rute rektal menunjukkan c max dan t max lebih lama dari sediaan syrup, hal ini disebabkan kelarutan ibuprofen yang rendah. Nanopartikel merupakan salah satu teknologi yang banyak digunakan untuk meningkatkan kelarutan suatu zat aktif. Ukuran partikel berskala nano, dapat membantu meningkatkan kelarutan ibuprofen serta memungkinkan pengurangan dosis. Penelitian ini bertujuan untuk memformulasi sediaan nanosuppositoria ibuprofen, serta menguji persen disolusi nanosuppositoria dibandingkan dengan suppositoria konvensional. Formulasi nanosuppositoria ibuprofen terdiri dari komponen lipid ibuprofen dan komponen PEG mix (PEG 4000 : PEG 6000). Komponen lipid ibuprofen terdiri dari ibuprofen minyak VCO, tween 80 dan propilenglikol. Komponen lipid ini selanjutnya diuji karakteritik fisik, nilai transmitansi, ukuran partikel dan nilai zeta potensial, selanjutnya lipid ditambahkan pada komponen basis suppositoria. Respon yang diamati adalah waktu hancur, kekerasan, nilai evisiensi disolusi non instrinsik. Hasil uji menunjukkan nilai transmitan 91,98%, 92,99%, 93,26%. Ukuran partikel dan nilai zeta potensial FI = 107, 5 nm, FII 102 nm dan FIII 103 nm. Nilai zeta potensial -16,19 mV , -12,44 dan – 13,25mV pada komponen lipid. Hasil uji waktu hancur nanosuppositoria FI, FII, FIII yakni 12 menit, 11 menit dan10 menit. Kekerasan FI, FII, dan FIII yakni 1,53 kg, 1,43 kg dan 1,26 kg dan nilai evisiensi disolusi lebih tinggi dibandingkan suppositoria konvensional. Modifikasi nanosuppositoria ibuprofen memberikan pengaruh signifikan terhadap persen terdisolusi dari ibuprofen.

Kata Kunci: *Nanosuppositoria, Ibuprofen, Uji Disolusi*

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Introduction:

Fever has the benefit of fighting infection, but fever also has a negative impact including increased body metabolism, mild dehydration and discomfort in children. Fever management can be done by administering drugs and supportive therapy. Drugs that can be given for fever management include paracetamol, ibuprofen, or aspirin. Ibuprofen is a class of non-steroidal anti-inflammatory drugs (NSAIDs) that are often used as antipyretics in children. Ibuprofen is the most widely used non-steroidal anti-inflammatory drug (NSAID) for the treatment of inflammation, mild to moderate pain and fever in children, due to its good tolerability profile, making it the only NSAID approved for use in children older than 3 months (de Martino *et al.*, 2017).

In oral delivery, we find ibuprofen formulated in solid or liquid form. The low solubility of ibuprofen is a challenge in formulating ibuprofen in liquid or solid dosage form. Ibuprofen formulated in suspension form is formulated with the addition of suspending agent and solvent, in order to increase the solubility and stability of the suspension. The addition of sweeteners, flavors and colors is also necessary, so that the preparation is liked by children. However, recently solvents used at too high a concentration may cross the safety threshold for consumers. Ibuprofen is a BCS class II drug, for BCS class II drugs that have low solubility and high permeability, the dissolution rate is one of the factors limiting oral absorption. Some that affect the dissolution rate include gastric emptying factors, incomplete disintegration of solid dosage forms in the stomach (Hofmann *et al.*, 2020).

Another route of administration of ibuprofen is rectally, in the form of suppositories. Suppositories are a dosage form used to provide systemic and local effects. The general principle is that the suppository is inserted as a solid object and dissolves or melts in the body to deliver the drug that is received by the many blood vessels present locally. The advantages of this preparation are the drug is easily absorbed quickly through the mucous membrane, it is a convenient mode of administration for drugs that cause vomiting, irritate the gastrointestinal tract, and drugs that are destroyed at the acidic pH of the stomach, the suppository dosage form is useful when oral administration is not possible, it is suitable for unconscious patients, uncooperative patients, and patients suffering from severe vomiting. This preparation provides a rapid onset of action compared to the oral route because absorption of the drug through the rectal mucosa directly reaches the blood (avoiding first metabolism). Increased bioavailability can be achieved compared to oral dosage forms. The rectal route of administration offers a much more constant atmosphere for the drug to be absorbed compared to the oral route and there is no problem of the drug having an unpleasant taste and odor, as it does not need to be swallowed (Chandra Sekhara Rao G *et al.*, 2023). These dosage forms are more favorable than oral preparations and may be combined into LBDDS delivery forms. Lipid-based drug delivery systems (LBDDS) are formulations that contain drug substances dissolved or suspended in lipid excipients. One type of this delivery is lipid nanoparticulate carriers. Some of the advantages of this delivery are increased drug stability, high drug loading, incorporation of lipophilic and hydrophilic drugs. lack of carrier biotoxicity and relatively cost-effective. Lipid nanoparticles are categorized into two types according to their structure namely lipid nanoparticles-SLN and NLC. SLNs were developed with solid lipid composition only. Then, to upgrade to SLNs, NLCs were made representing a mixture of solid and liquid lipids, with solid lipids being predominant (Stefanov and Andonova, 2021). Nanoparticles are one of the technologies that are widely used to increase the solubility of an active substance. With nanoscale particle size, it can help increase the solubility of ibuprofen. In some studies, it shows the potential for dose reduction, after the preparation is modified into a nanoparticle preparation (Kannadasan *et al.*, 2020). This technology allows it to be utilized in the preparation of nanoparticle-based suppository preparations. This study aims to

formulate suppository preparations, with nanoparticle modification and see the percent dissolution results of nanosuppositories compared to conventional suppositories. Modifications were made to the formulation of ibuprofen into lipid form. Lipids consist of oil components, surfactants and cosurfactants, which in a certain ratio produce a mixture that does not separate and the lipid dispersion results are clear. A certain amount of ibuprofen will be loaded into the lipid and then, the transmittance value is tested as an initial screening of the formation of ibuprofen nanoparticle dispersion. The particle size, polydispersity index and zeta potential values of the ibuprofen lipids will be measured using PSA. The ibuprofen lipids will be formulated with suppositroia base. The suppository bases used are polyethylenglycol 400 and 6000. The challenge of making suppositories is in the hardness and melting time test, so in this study, optimization will be carried out on the lipid component and the mixture of polyethylene glycol 400 and 6000 and see the physical characteristics of the three formulas, then the percent of non-intrinsic dissolution will be observed. This research is expected to be an alternative to existing preparations, so that a reduction in the dose of administration can be possible without reducing the activity of the active substance in the preparation.

Methods:

Equipment

Suppository molding apparatus (Mettler Toledo), suppository hardness tester, Disintegration time tester (Shanghai develop bj-2), digital balance (Shimadzu), UV Vis spectrophotometer (Shimadzu), dissolution tester (Electrolab), PSA (Malvern).

Materials

Virgin Coconut Oil (NHR Organics Oils®), tween 80 (LUG®), propylenglycol (DOW®), ibuprofen (Phapros®), PEG 400 (Subur Kimia Jaya®), PEG 6000 (Subur Kimia Jaya®), magnesium chloride (Smart Lab®), calcium chloride (Smart Lab®), potassium chloride (Smart Lab®), sodium chloride (Smart Lab®), sodium hydrogen carbonate (SCM group®), CO_2-free distilled water.

Preparation of Ibuprofen Lipids

Oil phase, surfactant and cosurfactant which we call lipid phase. Weighed and mixed vortexed, added drug substance. A total of 10.0 mg of ibuprofen into 1 ml of oil, surfactant or cosurfactant then vortexed for 5 minutes, sonicated for 10 minutes and incubated at 40°C for 5 minutes, done as many as three consecutive cycles. This method is a modification of previous research by Handoyo (2019) (Handoyo Sahumena et al, 2019)

Ibuprofen Lipid Assay

Loading drug

The assay was performed by dissolving 10.0 mg of ibuprofen into 1 ml of lipid, vortexed for 10 minutes, sonicated for 15 minutes and incubated at 40°C for 5 minutes, performed for three consecutive cycles. The lipid and ibuprofen mixture was centrifuged at 3000 rpm for 5 minutes to separate the supernatant from the lipid. The supernatant was diluted with HCl solution pH 1.2 and read on a UV Vis spectrophotometer. By entering the absorbance value into the line equation, the amount (mg/ml) of unloaded ibuprofen will be known. By knowing the loading drug of each formula, then the lipid preparation of ibuprofen can be prepared and used for testing the transmittance value, particle size, zeta potential.

Transmittance test

The test was conducted using the USP XXII standard dissolution apparatus II. The experiment was conducted at 37 ± 0.5°C, with the paddle rotating at 50 rpm. One milliliter of ibuprofen lipid was added to each dissolution tube containing 500 ml distilled water. The resulting emulsion was taken with a syringe, inserted into a cuvette and read the transmittance value using a UV-Vis spectrophotometer. The transmittance value of each formula was measured using UV-Vis spectrophotometry with distilled water as a blank, at a wavelength of 650 nm.

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Globule Size

Globule measurement was done after ibuprofen lipid was diluted into distilled water. Lipid ibuprofen as much as 0.1 ml was dissolved in 50 ml distilled water, stirring was done with the help of a magnetic stirrer, for 5 minutes. Determination of globule size using *Particle Size Analyzer* (PSA) (Aspadiah et al., 2020).

Ibuprofen Nanosuppository Formula

Suppository preparations were made with the components shown in Table 1.

The formula consists of two main components, namely the lipid component and the base component.

Table 1. Ibuprofen lipid formula

Lipid Component		Comparison
Oil	VCO	1
Surfactan	Tween 80	10
Cosurfactan	Propylenglycol	1

Table 2: Ibuprofen nanosuppository formula

Formula	Lipid (%)	PEG 400 (%)	PEG 6000 (%)
I	17	58.1	24.9
II	22	54.6	23.4
III	27	51	22

Evaluation of Ibuprofen Nanosuppository Preparation Characteristics

Organoleptical Test of Nanosuppositories

Color observation and surface characteristics of suppositories. The following can be checked: brilliance, dullness, mottling, cracks, dark regions, axial, cavities, bursts, air bubbles, holes (Chandra Sekhara Rao G *et al.*, 2023).

Weight Uniformity Test

The test was carried out by weighing 10 suppositories and recording the weight (Špaglová *et al.*, 2021).

Hardness Test

Suppositories were taken and placed in a hardness tester, at 25°C. additional load was applied, until the suppository cracked and recorded the time the suppository cracked (Abbaspour *et al.*, 2022).

Disintegration Time Test of Ibuprofen Nanosuppositories

Suppositories were placed into a tablet disintegration device containing 700 mL of water with the temperature maintained at 37°C (Chandra Sekhara Rao G *et al.*, 2023).

Dissolution Test of Ibuprofen Nanosuppositories

Dissolution speed test of each formula using a type of device (Huizinga model for non-intricate). The receiving medium liquid used was carbon dioxide-free water as much as 500.0 ml with a temperature of 37 ± 1°C, stirred at a speed of 100 rotations per minute. Then the dissolved ibuprofen content was analyzed by UV vis spectro and then the absorbance was measured (previously conducted preliminary analysis experiments, standard curves, reading times and others). The amount of drug released from the suppository into the medium was calculated based on the standard curve that had been made, while the results of the drug release speed were expressed in DE (%). The medium used was phosphate-buffered saline pH 7.4 at 37ºC. Preparation of Artificial Intestinal Fluid (AIF). Weighed magnesium chloride 0.1523 grams, calcium chloride 0.1470 grams, potassium chloride 0.0931 grams, sodium chloride 1.7550 grams, sodium hydrogen carbonate 0.4200 grams, dissolved in CO2-free distilled water to 500 ml. Check at pH 6.8 (Basel, 2005).

Results:

Screening of Oil, Surfactant, and Cosurfactant Component Comparison

In the formula with the ratio of oil, surfactant, and cosurfactant (1:10:1), a homogeneous lipid mixture was produced, which did not separate and the dispersion was clear.

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Figure 1. Lipid

Lipids were then added with ibuprofen. Lipids that have been added ibuprofen, then conducted physical characteristics test.

Ibuprofen Lipid Physical Characteristics Test

Table 3. Loading drug test results and lipid transmittance values of ibuprofen

Formula	*Loading drugs* (mg)	%T
FI	59.9±0,0007	91.98±0.557
F II	79.93±0,1527	92.99± 0.601
F III	100.03±0,642	93.26±0.585

Globule Size and Zeta Potential

The particle size of ibuprofen lipids FI = 107.5 nm, FII 102 nm and FIII 103 nm. The zeta potential values were -16.19 mV, -12.44 and -13.25 mV.

Suppository Preparation Results

Table 4. Organoleptic of Ibuprofen Nanosuppository Preparation

Formula	Shape	Colour	Weights (grams)
F I	Torpedo	White	2.4±0.05
F II	Torpedo	White	2.3±0.1
F III	Torpedo	White	2.3±0.1

Figure 2. Ibuprofen nanosuppository

Hardness test

Table 5. Hardness of Nanosuppositories

Formula	Hardness (kg)	Time
F I	1.53 ±0.1154	4 minutes 32 seconds
F II	1.43±0.1152	3 minutes 41 seconds
F III	1.26±0.1154	2 minutes 56 seconds

Table 6. Nanosuppository Disintegration Time Test Results

Formula	Disintegration Time
F I	12 minute 47 seconds ±11,503
F II	11 minute 14 seconds ±37,44
F III	10 minute 51 seconds ±18,55

Nanosuppository Melting Point Test Results

Table 7. Melting Point Test Results

Formula	Melting point (ºC)
FI	38.66±0,573
FII	39.15±0,07
FIII	38.76±0,665

Dissolution Test Results of Ibuprofen Nanosuppositories

Table 8. Dissolution Test of Ibuprofen Nanosuppositories

Tube	% Disolved			
	FI	FII	FIII	suppository conventional
1	106.17	79.63	90.58	78.15
2	88.66	99.33	93.06	72.96
3	126.77	90.83	81.01	75.18
4	111.32	119.02	89.66	86.8
5	96.38	85.03	85.33	89.28
6	93.29	100.87	91.82	76.17

Discussion:

Ibuprofen Lipid Physical Characteristics Test

Drug loading test and transmittance

Loading drug test, done by adding ibuprofen as much as 10 mg in 1 ml of lipid, tested for transmittance, added back 10 mg, retested transmittance value. In the addition of ibuprofen more than 160 mg/mL the dispersion

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results show a small transmittance value, so the limit of adding ibuprofen is seen from the transmittance value. Transmittance test is a test conducted to determine the clarity of the ibuprofen lipid formula dispersed in the media. The higher the clarity value measured by %T on the spectrophotometer, it can be concluded that the smaller the size of the globules in the lipid formula. The transmittance value of >99% indicates the clarity of the emulsion results and in the study obtained the transmittance value in the aquadest media which got the largest transmittance value was FIII.Serve summary results in the form of graphs and numbers, compare with previous studies, if quantitative research provides statistical tests, focus on what needs to be emphasized, use clear language and not cause multiple meanings.Answer the research problem, support and maintain the answer with the results, compare with the results of the relevant research, state the limitations of the study conducted, state the importance of the findings, find or come up with newness and submit further research.

Globule Size and Zeta Potential

The particle size of ibuprofen lipids FI = 107.5 nm, FII 102 nm and FIII 103 nm. The zeta potential values were -16.19 mV, -12.44 and -13.25 mV. We searched for articles related to the size range of nanoparticles, and several articles mentioned nanoparticles are preparations with particle sizes in the range of 1-100 nm (Sravani, Renuka and Praveen, 2020), 20-150 nm (Katya M et al, 2022) or 10-1000 nm (Kannadasan *et al.*, 2020).

Organoleptic Nanosuppository Test

To determine the effect of the percentage ratio of lipids, PEG 400 and 6000 on the formula, the physical characteristics of nanosuppository preparations were tested. The combination of PEG 400 and PEG 6000, gives the appearance of the color of the suppositories as shown in the figure. All nanosuppository formulas have a white color, torpedo-shaped with a smooth surface without holes and streaks.

Hardness Test

The hardness test was carried out to see the hardness of nanosuppositories. Assess the effect of adding lipids to the base, combination of PEG 400 and PEG 6000.

Nanosuppositories are expected to have an acceptable hardness during handling and shipping. The highest hardness was shown in formula I, where fewer lipid components were dispersed into the suppository base. Nanosuppositories FII and FIII had lower hardness. PEG is a stable base at room temperature. The results of the preparation showed that PEG is able to mix with lipid components, at certain concentrations. The results of the nanosuppository hardness test can be seen in Table 5. The hardness of the three formulas has a significant difference, the higher the lipid concentration the lower the hardness. The hardness test results showed significant differences between the nanosuppository preparation formulas (sig<0.05). This is due to the different percentage of lipids in each formula.

Disintegration Time

Suppository bases consist of water-soluble bases and oil-soluble bases. The drug released from water-soluble bases (such as PEG) is greater compared to oil-soluble bases. PEG 6000 is a high molecular weight suppository base (MW: 6000). The effect of changing the level of PEG as a suppository base on physical and release properties was studied. This was done by changing the levels of PEG 6000 and PEG 4000 bases, but still with the same ratio. The increasing amount of lipids, of course, makes the PEG content smaller, this causes the suppository disintegration time to be faster. Several studies usually make similar changes in proportions to get the best characteristics (Alwan and Al-Akkam, 2019). The results of the disintegrtion time test showed significant differences between the nanosuppository preparation formulas (sig<0.05). This is due to the difference in the percentage of lipids in each formula, the higher the lipid concentration, the faster the suppository is released in the media.

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Nanosuppository Melting Point Test Results

FI, II and III nanosuppositories have the same melting point. The three formulas use a combination of PEG 400 and 6000 in the same ratio, namely 70:30. The melting temperature of the three nanosuppositories shows that this preparation will be stable at room temperature. Statistical test results showed insignificant differences between nanosuppository preparations (sig>0.05).

Dissolution Test Results of Ibuprfen Nanosuppositories

Dissolution is an important stage to determine the release of active substances from preparations. Drugs with low solubility are not favorable when formulated into suppository preparations, due to fluid limitations in the rectal area (S.Hargoli, J.Fard, S.H.Azarm, S.Ghanbarzadeh, 2013). The base of the suppository can affect the speed of drug release from the suppository. Choosing the right base will produce suppositories with good physical characteristics (Marchaban, 2015). The non-intrinsic method is the method used in this dissolution process. In a study by Marhaban, showed that the non-intrinsic method gave a higher release value than the intrinsic method. The results of the dissolution test of the three formulas showed that the average of the 6 tubes in FI, FII, FIII 103.76%, 95.78% and 88.57%. In conventional suppository preparations, the percent dissolved was 79.75%. The dissolution test results showed significant differences between suppository preparations and nanosuppositories (sig<0.05). The results of the nanosuppository dissolution test and conventional suppositories can be seen in table 8. Previous studies have shown that ibuprofen suppository preparations were found to have lower c max and t max values than ibuprofen syrup preparations, this is due to the low solubility of ibuprofen in the media (Silvia, 2011), although in syrup preparations the solubility of ibuprofen has been increased with the help of solvents or suspending agents. Nanoparticle modification in suppository preparations aims to increase the solubility of ibuprofen. Selection of the right base is also a factor that affects the dissolution results of suppositories. Hydrophilic bases promise faster release, compared to lipophilic bases (Hua, 2019).

Conclusions:

ibuprofen nanosuppository preparations have a higher percent dissolved than conventional suppository preparations.

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References:

Abbaspour, M. *et al.* (2022) 'Development and Evaluation of Vaginal Suppository Containing Althaea officinalis L. Polysaccharide Extract', *Brazilian Journal of Pharmaceutical Sciences*, 58. Available at: https://doi.org/10.1590/s2175-97902022e20868.

Alwan, L.A.H. and Al-Akkam, E.J. (2019) 'Formulation and in vitro evaluation of piroxicam conventional and hollow suppositories', *International Journal of Applied Pharmaceutics*, 11(3), pp. 63–71. Available at: https://doi.org/10.22159/ijap.2019v11i3.31861.

Chandra Sekhara Rao G *et al.* (2023) 'A review on suppositories', *GSC Biological and Pharmaceutical Sciences*, 25(1), pp. 186–192. Available at: https://doi.org/10.30574/gscbps.2023.25.1.0429.

Handoyo Sahumena, M., Suryani, S. and Rahmadani, N. (2019) 'Formulasi Self-Nanoemulsifiying Drug Delivery System (SNEDDS) Asam Mefenamat menggunakan VCO dengan Kombinasi Surfaktan Tween dan Span', *Journal Syifa Sciences and Clinical Research*, 1(2), pp. 37–46. Available at: https://doi.org/10.37311/jsscr.v1i2.2660.

Hofmann, M. *et al.* (2020) 'In vitro prediction of in vivo absorption of ibuprofen from

suspensions through rational choice of dissolution conditions', *European Journal of Pharmaceutics and Biopharmaceutics*, 149(December 2019), pp. 229–237. Available at: https://doi.org/10.1016/j.ejpb.2020.02.009.

Hua, S. (2019) 'Physiological and pharmaceutical considerations for rectal drug formulations', *Frontiers in Pharmacology*, 10(October), pp. 1–16. Available at: https://doi.org/10.3389/fphar.2019.01196.

Kannadasan, D.M. *et al.* (2020) 'a Review: Nano Particle Drug Delivery System', *International Journal of Pharmaceutical Sciences and Medicine*, 5(12), pp. 46–58. Available at: https://doi.org/10.47760/ijpsm.2020.v05i12.008.

Katya M.Aguilar-Perez, Dora I, Medina, Roberto Parra-Saldivar, H.M.Ni. (2022) 'Nano-Size Characterization and Antifungal Evaluation Essential Oil Molecules-Loaded Nanoliposomes'.

Marchaban (2015) 'Evaluasi pelepasan obat dari supositoria basis lemak : perbedaan antara metode disolusi intrinsik dan non-intrinsik', *Majalah Farmasi Indonesia*, 15(4), pp. 163–168.

de Martino, M. *et al.* (2017) 'Working Towards an Appropriate Use of Ibuprofen in Children: An Evidence-Based Appraisal', *Drugs*, 77(12), pp. 1295–1311. Available at: https://doi.org/10.1007/s40265-017-0751-z.

S.Hargoli, J.Fard, S.H.Azarm, S.Ghanbarzadeh, P.Z.M. (2013) 'Preparation and In Fitro Evaluation of Naproxen Suppositories', *Indian.J.Pharm.Sci* [Preprint].

Silvia, S. (2011) 'Uji Disolusi Komparatif Tablet Ibuprofen Generik Bermerek dan Generik Berlogo', *Fakultas Farmasi* [Preprint]. Available at: http://dx.doi.org/10.1038/ni.1913%0Ahttp://dx.doi.org/10.1016/j.dci.2013.08.014%0Ahttp://dx.doi.org/10.1186/s13071-016-1819-4%0Ahttp://dx.doi.org/10.1016/j.actatropica.2017.02.006%0Ahttp://dx.doi.org/10.1038/s41598-017-09955-y%0Ahttp://dx.doi.org/10.1016/.

Špaglová, M. *et al.* (2021) 'Possibilities of microemulsion application in rectal administration of indomethacin', *European Pharmaceutical Journal*, 68(1), pp. 94–97. Available at: https://doi.org/10.2478/afpuc-2021-0012.

Sravani, K.S., Renuka, K. and Praveen, K. (2020) 'Nano particles : A current review', 9(7), pp. 200–202.

Stefanov, S.R. and Andonova, V.Y. (2021) 'Lipid nanoparticulate drug delivery systems: Recent advances in the treatment of skin disorders', *Pharmaceuticals*, 14(11). Available at: https://doi.org/10.3390/ph14111083.