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Optimization of Microgel Formula Combination of Snail Mucus and Catechin to Accelerate Wound Closure

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ABSTRACT

Incised wound healing is a crucial process that requires effective treatment solutions. A microgel containing snail mucus and catechin seems a promising approach to accelerate healing and improve recovery outcomes. This study aimed to develop a microgel preparation contain snail mucus (*Achatina fulica*) and catechin. Formulation design is assisted using the Design Expert SLD method. The optimum formula was achieved with a carbopol to TEA ratio of 1.589:0.411, with estimated values of pH (4.506), viscosity (18,873 cPs), spread ability (5.477 cm), and adhesion (2.068 second). These estimated values showed no significant difference from the actual values obtained in the laboratory experiments. To evaluate the quality of the preparation, in vivo testing was performed on white mice, and the data were analysed using one-way ANOVA. The snail mucus and catechin microgels were proven to be effective in treating deep incision wounds.

INTRODUCTION

Deep wounds in the skin are usually caused by surgery, caesarean, accident, or trauma. Wounds that are not treated properly will have long-term healing and can even accumulate scar tissue. Scars can disrupt the appearance and often make the sufferer less confident. In addition, wounds that decelerate to close can cause many infections, and then some drugs such as corticosteroid drugs can disrupt wound closure. The other way to remove accumulated scars is by removing the skin tissue through operation. However, it is neither less effective nor has a high potential for scar recurrence and there can even be a buildup of skin tissue (Komalasari et al., 2022; Pudiastuti & Aisiyah, 2014).

An innovative alternative treatment being developed is a microgel preparation with active substances from snail mucus and catechin, which is known to have a therapeutic effect. A concentration of 2% snail mucus can accelerate the wound closure process. Snail slime contains active substances called *acharan sulfate* (proteoglycan) which can binder and reservoir for basic fibroblast growth factor (bFGF) that is excreted on the extracellular matrix (ECM). The ECM produces bFGF which stimulates activation of fibroblast and forming new red blood cell formation following injury. In comparison, the research conducted by (Dooley et al., 2012) showed that a concentration of 1-100 μM epigallocatechin-3-gallate (EGCG) was able to reduce type 1 collagen production induced by TGF-β, fibronectin, and CTGF. Another study by (Song et al., 2023) supports the benefits of catechins in reducing proliferation by 1 gram of EGCG can enhance the inhibition of hypertrophic scar tissue formation, attenuate collagen area fraction, and significantly inhibit

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mRNA expression of TGF-β1, type 1 collagen, alpha-SMA, and eNOS.

Gel preparations with micro size are known to reach the target with faster action. In addition, these preparations can respond to biomedically relevant changes such as pH and body temperature. Preparations in the form of micro are considered quite comfortable when used, give a cooling sensation when applied to the skin, have good drug release, and are easy to wash (Nugroho et al., 2020; Shoviantari et al., 2021).

In making preparations with the optimum formula, it assisted by using Design Expert software using the Simplex Lattice Design method (Handayani et al., 2018). The main objective is to help determine the ratio of the Carbopol and triethanolamine (TEA) that are crucial points of the preparation, both greatly affect pH, viscosity, spread ability, and adhesion of the microgel preparation. The optimization range of Carbopol 940 according to (Rowe et al., 2009) is 0,5-2% while according to (Tsabitah et al., 2020) the range of TEA used is from 0,4-1%.

METHODS

The research was conducted in the University Muhammadiyah of Purwokerto (UMP) laboratory approximately 4 months. The study used an experimental method that followed ethical guidelines, as approved by the UMP Health Research Ethics Committee (No. KEPK/UMP/128/V/2024) for the use of test animals. Its aim was to assess the effectiveness of snail mucus and catechins in microgel formulations for accelerating wound healing.

Table 1. The Results of Eight Run Formula from Simplex Lattice Design (SLD)

Std	Run	Carbopol (%)	TEA (%)
2	1	1.5	0.5
6	2	1.6	0.4
1	3	1.6	0.4
7	4	1.5	0.5
8	5	1.55	0.45
5	6	1.525	0.475
3	7	1.55	0.45
4	8	1.575	0.425

Research Material

Twenty snails weighing 40-50grams that have been fasted for at least 1 day (24 hours) obtained from Banyumas area; pure catechin (analytical grade, Sigma Aldrich); Carbopol 940, TEA, nipagin, propylene glycol, glycerine, aqua dest, all of them are technical grade (Bratachem).

Research Tools

Mortar, stamper, measuring cup, stirring rod, water bath (Memmert®), glassware (Pyrex®), analytical balance (Shimadzu®), ultrasonic homogenizer (Shimadzu®), Brookfield viscometer, Particle Size Analyzer (Horiba®).

Preparation of Snail Mucus

The snail that has been fasting for one day is then stimulated to secrete mucus by rubbing the gastropod part of the snail using a stirring rod. The collected snail mucus was then filtered and frozen to prevent degradation of the active substances.

Creating the Design of Experiment

Data will be inputted by entering the range of the low and high levels of Carbopol and TEA as independent variables and and the responses (pH, viscosity, spread ability, and adhesion force) as dependent variables to Design Expert software. The software will generate a design of experiment containing runs with compositions that are randomly determined based on the previous input, as shown in **Table 2.**

Preparation of Formulation Base

Carbopol was developed in a hot mortar using hot distilled water and stirred until fully expanded. Gradually add TEA according to the run formula. Mix the solution consisting of nipagin, distilled water, propylene glycol, and glycerine in the first 30 minutes using an ultrasonic homogenizer with probe size Φ6 (1/4) frequency 20-25KHz at 500W. Then in the next 30 minutes add the mixture with catechins and snail mucus and mix again using the same method. After that, mix it into the base that contains a mixture of carbopol, TEA, and aqua dest that has been homogenized earlier.

Table 2. Actual Design of Snail Mucus and Catechin-Loaded Microgel Optimization with Response Values

Run	Component (independent variables)			Response (dependent variables)		
	Carbopol (%)	TEA (%)	pH	Viscosity (cPs)	Spread ability (cm)	Adhesion force (second)
1	1.5	0.5	5	11460	5.1	1.12
2	1.6	0.4	4	19800	5.5	2.36
3	1.6	0.4	4	18900	5.6	2.38
4	1.5	0.5	5	9300	5	1.27
5	1.55	0.45	6	13420	5.3	1.39
6	1.525	0.475	6	15640	5.2	1.3
7	1.55	0.45	5	17380	5.2	1.48
8	1.575	0.425	5	18440	5.4	1.73

All ingredients except carbopol and TEA in each formula have the same concentration, namely snail mucus as an active substance to accelerate wound closure by as much as 2%, catechin as an agent to inhibit proliferation by as much as 2.5% snail mucus to accelerate wound closure by increasing fibroblast production, nipagin as a preservative as much as 0.2%, glycerine as a binder as much as 10%, propylene glycol as a humectant as much as 10%, aqua dest in ad to 100mL (Srivastava et al., 2023).

Verification of Preparation Mixing Method

Mixtures of solutions other than bases mixed using an Ultrasonic Homogenizer were checked for particle size using Particle Size Analyzer and Zeta Potential.

Evaluation of The Quality of the Preparation Using 4 Test Responses

pH Testing

The pH of the samples were measured using a universal pH indicator. The acceptability of the pH of the preparation is in the range of 4.5-6.5 (Rahmatullah, 2020).

Viscosity Testing

The viscosity of the samples were measured using a Brookfield spindle 4 viscometer at 30rpm. The viscosity range taken is 9300-19800 cps (Murdiana et al., 2022).

Determination of Spread ability and Adhesion Force

The spread ability test was carried out by weighing 1 gram of microgel preparation placed on a glass with a volume of 20×20cm. A weight of 50 grams, 100 grams, 150 grams, 200 grams, and 250 grams was then applied alternately, with a 1-minute interval between each application. Measure the diameter of the ointment sequence at each different weight (Yati et al., 2018).

The adhesion test is carried out with as much as 0.25 grams of gel preparation that has been weighed and then placed in one of the object glasses on the adhesion test device. Cover the object glass with another object glass and then give a 1kg load and let stand for 5 minutes. Then in the next minute pull the glass object with a load of 80 grams and record the time (Rohmani & Kuncoro, 2019).

Determination of Optimum Formula

After all preparation tests are carried out, then enter the test data into Design Expert to determine the analysis method for each test response. Set the acceptance requirements in the optimization section of the numerical section. After that, go to the numerical section in the report (solution) section to see the optimum formula.

In-vivo Testing

The snail mucus and catechin (SMC) microgel that has been made will prove its effectiveness through in vivo tests on female white rat test animals. Four test groups of four animal each were tested, namely the untreated group (negative control), the positive control group using polyhexanide 0.1%, the vehicle control given the microgel base, and treatment group given SMC microgel. The number of test animals per group was calculated based on Federer's formula, (t-1)(n-1)≥15 with t representing the number of test groups, and n representing the number of samples per group.

The test model in rats is an incision wound. Rats were induced with ketamine anaesthetic to facilitate treatment (Ousey et al., 2018). After the rat is unconscious, lay the rat down and shave the abdominal area, and then sterilize it using an alcohol swab, measuring approximately 3cm long for transverse treatment. The rat is then slashed in the measurement area, stabbing with depth until it reaches the muscle layer. After that, suture the wound and apply each group according to its administration. Wound healing was monitored for 20 days after treatment. Data on the percent of wound healing will then be verified using the ONE-WAY ANOVA test (Gaikwad et al., 2022; Nilawati Usman et al., 2024).

RESULT

The formula obtained with the help of Design Expert software with a range of low and high Carbopol (1.5-1.6%) and TEA (0.4-0.5%) resulted in 8 formulations estimated to achieve the optimal preparation with four main test responses namely viscosity, spread ability, adhesion, and pH.

The verification of the preparation methods on stability and particle size was conducted using Particle Size Analyzer (PSA). The results showed an average droplet size of 593 ± 21.546 nm. The zeta potential value was -30.0667 ± 2.2189 mV, and the PDI value was 0.9473 ± 0.2532. These findings indicate that microgel preparation is stable, as confirmed based on particle size and zeta potential (Baby et al., 2015; Marsili et al., 2021).

The SMC microgel is carried out four main tests to determine its physical quality. The test equations obtained are viscosity, η (1), spread ability (2), adhesion (3), and pH (4) respectively:

Y_{η} = +27111.25A-58844.30556B (1);

Y_{s} = +1.38852A+0.326412B (2);

Y_{a} = +6.36435A+53.97862B-47.25043AB (3);

Y_{pH} = -9.38877A-115.398748B+98.71147AB (4).

A represents Carbopol B represents TEA, and AB represents the relationship between two materials. The optimum formula is obtained after analysing the results of the four main tests of 8 formulas. The optimum formula is known in the numerical section menu with Carbopol content of 1.589% and TEA of 0.411%. The estimated test results of the optimum formula were pH of 4.5; spread ability of 5.477cm; thickness of 2.069 seconds; and viscosity of 18,873 cPs. The optimum formula was then replicated three times and the organoleptically obtained preparation was clear yellow, with a distinctive smell and taste (**figure 1**). The results meet all test parameters and are not significant different from the estimates from the Design Expert.

Figure 1. The Results of Optimum formula

To prove the effectiveness of the preparation that has been made, in vivo tests are carried out on white-strained rat test animals according to the code of ethics. Each group of rats amounted to four rats. The grouping of white rats is based on differences in the administration of preparations. Group 1 (NC) is the negative control, rats are not given any topical preparation after wound suturing. Group 2 as a positive control (PC), rats were given wound healing drugs on the market with the Polyhexanide 0.1%. Group 3 as vehicle group 1 (VC), rats were given microemulgel base without active substances. In group 4 as in treatment group (TC), the rats were given the SMC microgel. All treatments were performed simultaneously. The percentage of wound healing was determined by measuring the length of the wound on days 5, 10, 15, and 20 divided by the length of the wound at the beginning of treatment. The data was then entered into SPSS for the One-Way ANOVA test.

DISCUSSION

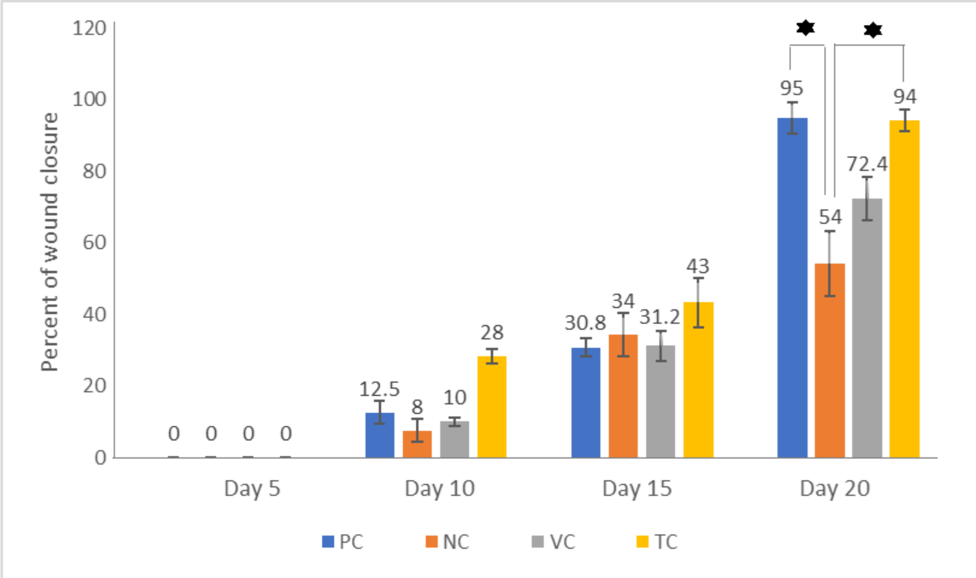

Figure 2. Percent of wound closure of various treatment group at various treatment period. Note: PC = positive control (Polyhexanide 0.1%), NC = negative control (untreated group); VC = vehicle control (microgel base), TC = (SMC microgel). The results of wound healing in terms of wound closure area within 20 days are expressed as mean ± SD (*n=3*), asterisk line on day 20 represented statistically different values between the NC and TC, and between NC and PC, with p<0.05 by Bonferroni tests.

Based on equation (1) carbopol has the greatest effect on increasing viscosity. This is due to the nature of carbopol when dissolved, it will form a three-dimensional structure that binds water molecules so that in the same volume of solvent with different carbopol concentrations, it will affect the viscosity of the preparation (Pradita & Wahyuni, 2023).

Equation (2) shows that the increase in spread ability is most influenced by carbopol as shown by the coefficient value of +1.38852. In this equation, the interaction between carbopol and TEA produces a coefficient with a positive value, which means that the use of carbopol and TEA together can increase spread ability. The use of carbopol in large quantities indirectly affects the viscosity of the preparation. This is because carbopol has high hydrophilicity so the use of large levels affects the sturdiness of the texture of the preparation so that it will narrow the diameter of the spread.

Equation (3) shows that the increase in the adhesion of the preparation is influenced by TEA, which is shown by the coefficient value of +53.97862. The increase in the adhesion of the preparation by TEA can occur because TEA as a base neutralizes the carboxyl group of carbopol, the carboxyl group on carbopol will dissociate to form a more cohesive and stable network, making the gel easier to stick to the skin. The interaction between Carbopol and TEA shows a negative coefficient value, indicating that if the concentrations are not optimized, adhesion may be reduced. Additionally, excessive TA increases the pH, and a higher pH can compromise the gel's cohesiveness, ultimately decreasing its adhesion. which means that it can reduce adhesion if the concentration is not optimal. The use of TEA in large amounts raises the pH. A gel with a high pH can reduce cohesiveness, thus reducing gel adhesion.

Equation (4) demonstrates that the pH of the preparation decreases as a result of TEA, with a coefficient value of -115.398762. TEA acts as a base to neutralize Carbopol, so the using of small amounts of Carbopol can help lower the pH of the preparation. The interaction between carbopol and TEA produces a positive coefficient value which indicates that the combination of the two together can have a positive effect on the preparation with the optimal percentage and ratio.

The results of testing the optimal preparation (three replications) were analyzed using SPSS with a One-Sample T-test. The pH showed a significance of 0.677; viscosity had a significance of 0.157; spread ability had a significance of 0.22; and adhesion had a significance of 0.001. Three out of the four tests had a p-value greater than 0.05, with the exception of adhesion which was significantly different.

Referring to **Figure 2**, the data days 20 obtained were then processed in SPSS for the One-Way ANOVA test and obtained a significance between the vehicle control group (VC) (which was given microgel base) and negative control (NC) (untreated group) with

Figure 3. Photographic images of wound healing at various treatments on days 5, 10, 15, 20. NC= Negative Control; PC= Positive Control; VC= Vehicle Control 1; TC= Treatment Control. The first row (3a to 3d) shows that there was no wound closure in any of the groups on day 5. In the second row, on day 10, the wounds in the NC (3e) and VC (3g) groups still appear gaping and red, while in the PC (3f) and TC (3h) groups, the wounds have started to close. In the third row, on day 15, the wounds in the NC and VC groups remain somewhat reddish and gaping, while the wounds in the PC and TC groups are slightly more closed. In the fourth row, on day 20, the wounds in the NC and VC groups are still somewhat red and have less smooth skin, whereas the wounds in the PC and TC groups are nearly closed, with smooth skin.

significancy of 0.007 ($p<0.05$); the difference was not significantly different between PC and TC. It can be said that TC gave almost the same effect as the positive control (given Polyhexanide 0.1%) ($p>0.05$).

From **figure 3,** the microgel containing 1% w/w snail mucus and 2% w/w catechin demonstrated enhanced wound healing, which was visible to the naked eye and almost complete within 20 days in the group treated with Polyhexanide 0.1% microgel. The almost complete wound healing was observable in TC groups within 20 days, while it required more than 20 days for the negative and vehicle control groups, so it was proven that the NC produced a much longer healing percentage than TC because the significance value was <0.05.

CONCLUSIONS

This study investigates the development of an optimized microgel formulation combining snail mucus and catechin to accelerate wound closure. The results show that the microgel significantly enhances wound closure, achieving complete healing within 20 days. The formulation demonstrates promising potential for accelerating tissue repair while minimizing the risk of accumulation scar tissue.

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AUTHORS' CONTRIBUTIONS

IYA is supervisor 1 and corresponding author; AS as supervisor 2; AFA is the PKM team leader and main author; RKS is member one; ATT is member two; and LA is member three.

CONFLICT OF INTERESTS

The authors declare that is not a conflict of interest.

ETHICAL CONSIDERATION

This research was conducted and has meet the research ethics code issued on the 16th of May 2024 with Registration Number: KEPK/UMP/128/V/2024

BIBLIOGRAPHY

Baby, J. N., Pramod, K., John, S., Aji Alex, M. R., Suneesh, C. V., Kapoor, S., & Tahir, M. A. (2015). Preparation and Evaluation of Tunable Emission Zinc Oxide Quantum Dots for Gene Delivery. International Journal of Pharmaceutical Sciences Review and Research, 35(1), 191–194. https://globalresearchonline.net/journalcontents/v35-1/36.pdf

Dooley, A., Bruckdorfer, K. R., & Abraham, D. J. (2012). Modulation of Fibrosis in Systemic Sclerosis by Nitric Oxide and Antioxidants. Cardiology Research and Practice, 1(1), 191-194. https://doi.org/10.1155/2012/521958

Gaikwad, S., Birla, S., Ingle, A. P., Gade, A., Ingle, P., Golińska, P., & Rai, M. (2022). Superior in Vivo Wound-Healing Activity of Mycosynthesized Silver Nanogel on Different Wound Models in Rat. Frontiers in Microbiology, 13, 1–16. https://doi.org/10.3389/fmicb.2022.881404

Handayani, F. S., Nugroho, B. H., & Munawiroh, S. Z. (2018). Optimization of Low Energy Nanoemulsion of Grape Seed Oil Formulation Using D-Optimal Mixture Design (DMD). Jurnal Ilmiah Farmasi, 14(1), 17–34. http://journal.uii.ac.id/index.php/JIF

Komalasari, K. W., Ketut Kwartantaya Winaya, Putu Gde Hari Wangsa, & I Dewa Made Rendy Sanjaya. (2022). Keloids Treated with a Combination of Surgical Excision and Intralesional Corticosteroid Injection: a Case Report. Intisari Sains Medis, 13(3), 561–565. https://doi.org/10.15562/ism.v13i3.1504

Marsili, L., Dal Bo, M., Berti, F., & Toffoli, G. (2021). Thermoresponsive Chitosan-Grafted-Poly(N-Vinyl Caprolactam) Microgels Via Ionotropic Gelation For Oncological Applications. Pharmaceutics, 13(10), 1–26. https://doi.org/10.3390/pharmaceutics13101654

Murdiana, H. E., Putri, M. K., Rosita, M. E., Kristariyanto, Y. A., & Kurniawaty, A. Y. (2022). Optimization of Rice (Oryza Sativa L.) Type M/a Cream Dosage Formula with Variations of

Stearic Acid, Cetyl Alcohol and Triethanolamine. Jurnal Farmamedika (Pharmamedica Journal), 7(2), 55–63. https://doi.org/10.47219/ath.v7i2.161

Nilawati Usman, A., Sartini, S., Yulianti, R., Kamsurya, M., Oktaviana, A., Nulandari, Z., Agustin, D. I., & Fendi, F. (2024). Turmeric extract gel and honey in post-cesarean section wound healing: A preliminary study. F1000Research, 12, 1–14. https://doi.org/10.12688/f1000research.134011.2

Nugroho, A. A., Adianto, C., & Patria, Y. (2020). Nano-Androcerum: Wound Healing Gel Innovation from Binahong Leaf and Cinnamon Nanoparticles on Chronic Wounds. Bimfi, 7(1), 26–42. https://doi.org/https://doi.org/10.48177/bimfi.v7i1.11

Ousey, K., Djohan, R., Dowsett, C., Ferreira, F., Hurd, T., & Romanelli, M. (2018). Surgical Wound Dehiscence: Improving Prevention and Outcomes. World Union of Wound Healing Societies. Consensus Document, 4. 17-19. https://pure.hud.ac.uk/en/publications/surgical-wound-dehiscence-improving-prevention-and-outcomes

Pradita, E. Y., & Wahyuni, S. (2023). Nanogel Synthesis Of Chitosan-Alginate-Siam Orange (Citrus nobilisLour) Extract and Its Antibacterial Activity. Indonesian Journal of Chemical Science, 12(1), 58–69. https://doi.org/10.15294/ijcs.v12i1

Pudiastuti, & Aisiyah, S. (2014). Gel Formulation Combination Snail Slime (Achatina fulica Ferr) and Aloe vera as Active Material for Treatment of Burn. Jurnal Farmasi Indonesia, 11(2), 123–129. https://doi.org/10.31001/jfi.v11i2.63

Rahmatullah, S. . A. W. . & K. N. (2020). Effect of Various Concentrations of Hydroxy Propyl Methyl Cellulose (HPMC) on the Physical Stability of Tobacco Extract Gel (Nicotiana tabaccum L.) and its Activity against Streptococcus mutans. CHMK Pharmaceutical Scientific Journal, 3(3), 189–194. https://cyber-chmk.net/ojs/index.php/farmasi/article/view/847

Rohmani, S., & Kuncoro, M. A. A. (2019). Stability and Activity Test of Basil Leaf Extract Gel and Sanitizer. JPSCR : Journal of Pharmaceutical Science and Clinical Research, 4(1), 16-28. https://doi.org/10.20961/jpscr.v4i1.27212

Rowe, R. C. R., Sheskey, P. J. S., & Cook, W. (2009). Handbook Pharmaceutical Excipients, Sixth Edition. 1064. https://adiyugatama.wordpress.com/wp-content/uploads/2012/03/handbook-of-pharmaceutical-excipients-6th-ed.pdf

Shoviantari, F., Fajriyah, S., Agustin, E., & Khairani, S. (2021). Activity Test of Snail Slime Gel (Achatina Fulica) as Wound Healing. Jurnal Ilmiah As-Syifaa, 13(1), 12–19. https://doi.org/10.33096/jifa.v13i1.648

Song, Y., Wang, T., Yang, L., Wu, J., Chen, L., Fan, X., Zhang, Z., Yang, Q., Yu, Z., & Song, B. (2023). EGCG Inhibits Hypertrophic Scar Formation in a Rabbit Ear Model. Journal of Cosmetic Dermatology, 22(4), 1382–1391. https://doi.org/10.1111/jocd.15587

Srivastava, S., Saha, S., & Jakhmola, V. (2023). Nanogel: Types, Methods of Preparation, Limitation, Evaluation and Application-A Systematic Review. International Journal of Drug Delivery Technology, 13(4), 1631–1639. https://doi.org/10.25258/ijddt.13.4.77

Tsabitah, A. F., Zulkarnain, A. K., Wahyuningsih, M. S. H., & Nugrahaningsih, D. A. A. (2020). Optimization of Carbomer, Propylene Glycol, and Triethanolamine in the Formulation of Gel Preparation of Ethanol Extract of Moon Flower Leaf (Tithonia diversifolia). Majalah Farmaseutik, 16(2), 111-118. https://doi.org/10.22146/farmaseutik.v16i2.45666

Yati, K., Jufri, M., Gozan, M., & Dwita, L. P. (2018). Effect of Various Concentrations of Hydroxy Propyl Methyl Cellulose (HPMC) on the Physical Stability of Tobacco Extract Gel (Nicotiana tabaccum L.) and its Activity against Streptococcus mutans. Pharmaceutical Sciences and Research, 5(3), 133–141. https://doi.org/10.7454/psr.v5i3.4146