



DOI:

10.22301/IJHMCR.2231-2245.2140

Article can be accessed online on:

<http://www.ijhmcr.com>

ORIGINAL ARTICLE

INTERNATIONAL JOURNAL
OF HEALTH MEDICINE AND
CURRENT RESEARCH

LITERATURE REVIEW OF GEL FORMULA OPTIMIZATION WITH CARBOMER AND HPMC VARIATIONS AND ANTIBACTERIAL ACTIVITIES OF TELANG FLOWER EXTRACTS (*Clitoria ternatea* L.) AGAINST ACNE-CAUSING BACTERIA

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ARTICLE INFO

Article History:

Received 15th November, 2022

Received in revised form

20th November, 2022

Accepted 25th December, 2022

Published online 31th December,
2022

Key words:

Clitoria ternatea, antibacterial, the
combination of HPMC and
carbomer, Simple Lattice Design

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ABSTRACT

Background: Telang flower (*Clitoria ternatea*) contains active ingredients with pharmacological potential, including antimicrobials. In addition, when compared with a single base, the combination of HPMC and carbomer can form a better gel mass physically, high viscosity, good drug release and dissolution, and good bioavailability. The SLD optimization method was chosen because it is a (relatively) simple optimization method compared to other optimization methods and can be used for formula optimization in various amounts of different material compositions to produce an optimum formula and to reduce trial and error from a mixture of carbomer and HPMC materials in the formulation. Anti-acne gel preparations of telang flower extract (*Clitoria ternatea* L.).

Method Research is a systematic literature review study. The optimum formula for the gel preparation was obtained using the Simplex Lattice Design (SLD) method

Research Results of the analysis of the SLR showed that the extract of telang flower (*Clitoria ternatea* L.) could provide inhibition on *Staphylococcus aureus*, *Propionibacterium acnes*, and *Staphylococcus epidermidis* bacteria and the combination of HPMC and Carbomer could affect the physical properties of the gel preparation when compared to the use of a single base, a variety of HPMC and Carbomer can form a better gel mass physically, have high viscosity, good drug release and dissolution and good bioavailability.

Conclusion: the optimum formula for the combination of HPMC and Carbomer using the Simplex Lattice Design method can provide good physical properties in the form of organoleptic, adhesion, spreadability, pH, and viscosity and is not irritating

Citation: Heru Andika Tatuh¹, Ana Indrayati¹, Mimiek Murukmihadi² "Faculty of Pharmacy", *International Journal of Health Medicine and Current Research*, 7, (02), 2231-2245

PRELIMINARY

Acne begins with inflammation of the ducts of the skin's oil glands which can cause blockages in the flow of sebum secreted by the sebaceous glands on the surface of the skin so that an eruption appears on the surface of the skin, starting with blackheads. One of the factors that cause blockages in the oil glands is the bacteria *Staphylococcus epidermidis* *Propionibacterium acne*., and *Staphylococcus aureus*. (Wasitaatmadja, 1997).

Butterfly pea flower (*Clitoria ternatea*) contains several active ingredients with pharmacological potential, including antimicrobials. This potential as medicinal ingredients uncovers active compounds such as tannins, pLATANins, saponins, triterpenoids, phenols, flavonoids, alkaloids, anthraquinones, anthocyanins, flavonol glycosides, steroids, essential oils, and stigma-4- ena-3,6-dione. supported by extensive phytochemical studies. (Budiashi, 2017). In addition, kamila et al. (2009) conducted secondary metabolite phytochemical screening and found moderate flavonoids, platanins, and terpenoids from *Clitoria ternatea*

flowers. Treatment of acne is done topically with the principles of preventing blackhead formation, suppressing inflammation, and accelerating the healing of acne lesions. The preparation used to facilitate the use of butterfly pea flowers as an anti-acne is a gel preparation. The gel preparation was chosen because it feels light when applied to the skin, thereby increasing the comfort of use (Kindangen, 2018).

RESEARCH METHODS

A. *Systematic Literature Review*

1. *Literature Review*

A literature review is a data collection method by collecting data in the library, reading, recording, and processing research materials related to HPMC and Carbomer optimization using the SLD method in the Design Expert program, optimum physical stability of gel preparations from a combination of HPMC and Carbomer, antibacterial butterfly pea (*C. ternatea*) against *Staphylococcus aureus*, *Propionibacterium acnes*, and *Staphylococcus epidermidis* as well as irritation test of the HPMC and Carbomer combination gel.

The preparation of a good literature review must consider the stages in compiling and writing a literature review.

2. Stages of Literature Review

21 planning. Determination of Research Questions (RQ) that are appropriate to the research topic as a start in conducting SLR research. The intended RQ is a question in formulating the problem, and then the SLR protocol is prepared. The following are the research questions in this study:

RQ 1. What is the effect of the combination of carbomer and HPMC on the physical properties of the gel preparation?

RQ 2. What is the optimum combination of carbomer and HPMC in the preparation to obtain physical properties, including adhesion, spreadability, pH, and viscosity, using the SLD (Simplex Lattice Design) method?

RQ 3. Does the butterfly pea flower extract affect *Staphylococcus aureus*, *Propionibacterium acnes*, and *Staphylococcus epidermidis* bacteria?

RQ 4. What is the safety of the optimum formula of carbomer and

HPMC combination gel preparations with irritation test parameters?

22 Search process. The search process is used to find and obtain relevant data sources to answer research questions and references regarding other data. The data search process uses the Google Chrome search engine with the Google Scholar site address

(<https://scholar.google.com>), Pubmed

(<https://pubmed.ncbi.nlm.nih.gov>),

Directory of Open Access Journals

(<https://doaj.org>), Science Direct

(<https://sciencedirect.com>), and

GARUDA

(<https://garuda.ristekbrin.go.id>). Data

search is done by determining the combination of words in the problem formulation and using Boolean OR to enter alternative synonyms and Boolean AND to connect the main terms. Keywords for search engines can be seen in table 1.

Table 1. keywords google scholar, Pubmed, DOAJ, Science direct, and GARUDA

Code	Keywords
#1	Combination of <i>carbomer</i> and <i>HPMC</i> or combination of <i>carbomer</i> and <u>Hydroxypropylmethylcellulose</u>
#2	Optimization <i>carbomer</i> and <i>HPMC</i> or optimization <i>carbomer</i> and <u>Hydroxypropylmethylcellulose</u>

#3	<i>Simple Lattice Design or SLD</i>
#4	Antimicrobial or antibacterial or antibacterial agents or antibacterial activity
#5	<i>Clitoria ternatea</i> flower or butterfly pea flower
#6	<i>Staphylococcus aureus</i> or <i>S. aureus</i>
#7	<i>Propionibacterium acnes</i> or <i>P. acnes</i>
#8	<i>Staphylococcus epidermidis</i> or <i>S. epidermidis</i>
#9	irritation test parameters
#10	#2 and #3, #4 and #5, #4 and #5 and #6, #4 and #5 and #7, #4 and #5 and #8, #2 and #9

23 Inclusion and Exclusion Criteria. This stage is carried out to decide whether the data sources found are suitable for SLR research.

Table 2. Inclusion Criteria

Inclusion Criteria	Indonesian and English
	International Journal, Full Text
	Scopus-indexed journal, web of science, and DOAJ.
	Journals fall into the Q1–Q4 category according to SCIMAGOJR

Table 3. Exclusion Criteria

Exclusion Criteria	<i>Journal paper classified as systematic review</i>
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<i>Duplicate journal paper</i>
<i>Journal paper outside the theme of the research</i>

2.4 Assessment of Journal Paper Quality (Quality Assessment).

Journal paper quality assessment is an evaluation of journal paper data sources which will be included in research results with various questions as follows:

QA 1. Does the journal paper write down the antibacterial of butterfly pea flower against *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Propionibacterium acnes* bacteria?

QA 2. Does the journal paper write down the combination of HPMC and carbomer?

QA 3. Does the journal paper write down the optimization of HPMC and carbomer using the Simple Lattice Design method?

QA 4. Does the journal paper write an irritation test?

From each paper, an answer value will be given to each of the questions above. Y (Yes) for problems and methods that are by the Quality Assessment and T (No) for problems and methods that are not following the Quality Assessment.

25 Selection of primary data study results. The results of the preliminary data study were selected according to the inclusion and exclusion criteria based on the formulation of the problem or Research Question. The results obtained are made in the form of flowcharts using PRISMA 2009 flow diagrams.

26 Data Extraction. Journal papers that have been obtained according to the criteria are then extracted for data in tabular form, including the researcher's name, research title, year of publication of the journal, research subject, and main findings in the journal paper. Data extraction was carried out in stages according to the Research Question.

27 Data Analysis. Data analysis in this study was carried out by carefully reading the abstracts and full-text journal papers resulting from inclusion, then the results were extracted data, synthesized using a narrative method referring to Research Questions. research methods or techniques, special tools and materials -the materials needed in the research, the sampling technique and the method of data analysis are precise so

that they can be understood and repeated by other researchers.

RESULTS AND DISCUSSION

A. Search Process Results

Search Process results from Google Scholar, Pubmed, Directory of Open Access Journals (DOAJ), Science Direct, and GARUDA website addresses are displayed in a PRISMA diagram. Search results were selected based on inclusion criteria to include articles in the research results and exclusion criteria to see reports that were the same and not following the research. The search results on the Science Direct website found 1,358 articles matching the keywords. The search results on the Pubmed site found articles that match the keywords of 63 articles. The search results on the Directory of Open Access Journals (DOAJ) website found three articles that matched. The search results on the GARUDA website found articles that match the keywords of 20 articles. Finally, the search results on the Google Scholar site found 56,741 articles that matched.

All articles obtained were identified and then filtered according to the inclusion criteria, and 22 papers

were used in the study results that met the inclusion and exclusion criteria.

The literature review results of the antimicrobial *Clitoria ternatea* L found three journals explaining the antibacterial activity of *C. ternatea* L against *Staphylococcus aureus*. Kamila et al. (2009) researched the roots, stems, leaves, seeds, and flowers of the butterfly pea plant and tested various Gram-positive and Gram-negative bacteria, one of which was *Staphylococcus aureus*. The study said that flowers on butterfly pea plants have an inhibitory effect on *Staphylococcus aureus* bacteria with an inhibition of 13 ± 1 mm with MIC (Minimum Inhibition Concentration) > 100 and MBC (Minimum Bactericidal Concentration) > 100 .

Hutajulu *et al.* (2008), in their research, said that the content of phenol compounds in the butterfly pea flower had antibacterial activity; this was stated by carrying out antibacterial testing of the phenolic compounds extracted from the butterfly pea flower. The test was carried out by dividing the three concentrations of 1%, 3%, and 5%; of the three concentrations, the greatest inhibition was found at a concentration

of 5% with an inhibition of 0.87mm, at a concentration of 1%, an inhibition of 0.85mm, and a concentration of 3%. In inhibition of 0.84mm, the possibility of inhibition at a concentration of 3% decreased due to contamination from the air.

Niranjan et al. (2020) also conducted antibacterial research on several bacteria, one of which was *Staphylococcus aureus*, using methanol extract from butterfly pea flowers, and obtained an inhibition of 11mm. Ezzudin et al. (2018), who researched the potential of the butterfly pea tree in human health, also found the butterfly pea flower's antibacterial activity against several tested bacteria, one of which was *Staphylococcus aureus* with an inhibition of 10mm.

Khumairoh et al. (2020) tested the 96% ethanol extract of butterfly pea flowers against *Propionibacterium acnes* bacteria by doing three repetitions and obtaining an inhibition of 8.57 ± 0.61 mm at an extract concentration of 5%. Furthermore, research on testing nanoparticles of ethanol extract of butterfly pea flowers was also carried out by Islely et al. (2020) with a concentration of $17\mu\text{g}$

and 66µg against *Staphylococcus aureus* bacteria which had an inhibition of 16.23mm and 31.53mm while against *Staphylococcus epidermidis* with an inhibition of 26.37mm and 26.37mm and 36.73mm.

The literature review results regarding the combination of HPMC and Carbomer, where there were four journals obtained. Kouchak et al. (2019) conducted a pH design study on eye gel preparations using a combination of 0.1% HPMC and 0.1% Carbomer and then compared them with Dorzolamide HCl preparations. The results of testing the variety of 0.1% HPMC and 0.1% Carbomer obtained a pH value of 5.8, corresponding to the pH range of Dorzolamide HCl, 4-6. Jyothi et al. (2016) used a combination of HPMC and Carbomer, tested the physical properties of the combined gel preparations, and compared HPMC gel preparations and Carbomer gel preparations. The results of the physical stability test showed that the HPMC and Carbomer combination gel preparations were better.

Srividya et al. (2001) conducted a study combining HPMC and Carbomer. The results of this

study obtained a combination formulation of HPMC and Carbomer with an HPMC concentration of 1.5; 1.0; 1.0; 1.0 and Carbomer 0.3; 0.3; 0.4; 0.5 has a viscosity with a speed of 20rpm 3062.5; 2875.0; 3087.5; 4750.0 and has an average pH of 6, after three months of physical stability testing, the HPMC and Carbomer combination formulation remained stable. Sheshala et al. (2019) also tested the combination of Carbopol and HPMC in eye drug preparations. In formula five, the variety of carbopol 0.8 and HPMC 1.5 obtained transparent organoleptic results, pH in the range of 6.02, and a viscosity of 1209.00 ± 28.28 cP. Gels also stay longer in the field, 6 to 8 hours.

The combination of HPMC and Carbomer was also carried out by Singh et al. (2013); in their research, Singh compared various gel bases, and one used a combination of HPMC and Carbomer. Physical testing on the HPMC and Carbomer combination gel preparations carried out consisted of organoleptic, which in the physical properties test of the gel using organoleptic gave results in a transparent gel form. Homogeneity testing of the HPMC and Carbomer

combination gel preparations gave homogeneous gel preparations with no grains in the trial. The pH test on this preparation also showed results with a gel pH value of 6.88. Testing the spreadability of the HPMC and Carbomer 5cm combination gel and the viscosity of the combination gel preparation at 50rpm was 4450dPa.S. Stability test of HPMC and Carbomer combination gel preparations from day 0-day 90 had Percent Drug Content day 0 = 98.6% - day 90 = 97.9%.

HPMC and Carbomer optimization using the Simplex Lattice Design method. Rohman et al. (2020) obtained the desired optimal formula in the combination of 4.5% HPMC and 0.5% Carbopol, with all tests of their physical properties according to predetermined criteria. According to Murdiyani et al. (2013), the optimum composition of 80% Carbopol–20% HPMC resulted in an optimum dark green gel with a distinctive odor with an adhesion value of 50.06 seconds, spreadability of 6.820 cm², a viscosity of 41.667 poise and pH 4,567.

The optimal use of carbopol and HPMC in the betel leaf extract nanoparticle gel formulation was obtained at concentrations of 80.9%

and 19.1% (Saryanti et al., 2019). Natashya et al. (2014), in their research, said that the Simplex Lattice Design could be used to predict the effect of the Carbopol 940 and HPMC based on the physical and chemical properties of the gel. Sari et al. (2016) optimized the combination of HPMC and Carbomer on the physical properties of extract gel and methanol fraction of kesum leaves (*Polygonum minus Huds.*). The optimum formula for the methanol extract of kesum leaves combined with 0% HPMC and 100% Carbomer had the highest total with a total of 0.6; the optimum formula for the methanol fraction of kesum leaves with the highest total was found in the combined formula of HPMC 90% and Carbopol 10% with a total of 0.56, test physical of the optimum formula of the extract and methanol fraction of kesum leaves.

Sulaiman et al. (2018) The optimum formula for the combination of HPMC and Carbomer on citronella essential oil gel 4.0% HPMC and 1.0% carbopol, the physical properties test of the gel obtained a homogeneous gel with a pH value of 6.00 ± 0.00 , viscosity 280.00 ± 26.46 dPa.S, spreadability 9.36 ± 0.47 cm², and

adhesion 2.36 ± 0.10 seconds. Meanwhile, Murtiningsih et al. (2014) also optimized the combination of HPMC and Carbomer using the SLD method. Testing the physical properties of the optimum formula on the organoleptic test of brown-colored gel due to the influence of the extract and the gel homogeneity test contained grains because the extract was not mixed on the gel base, in the viscosity test, the average value of optimum gel viscosity was 426.66 cP, the average value on the adhesion test of 178.66 seconds, the average spreading power was 32.69cm², and the optimum gel pH value was 5.23.

Irritation test where Sugihartini et al. (2020) tested several formulas with a gel pH of FI 6.23 ± 0.15 , FII 5.9 ± 0.1 , and FIII 5.27 ± 0.12 , the formulas for the three gels were not irritating. Asngad et al. (2018) also conducted an irritation test on a banana stem hand sanitizer gel preparation which has a pH of 5.5, which is slightly acidic but is optimal for skin pH ranging from 4.5 to 6.5. Ningrum (2018) tested irritation on peel-off preparations with a pH of 5, and the results were not irritating. From the several journals, it can be

said that the optimum preparation for the combination of HPMC and Carbomer in table 6 is not irritating because it is still in the skin pH range, overall the gel has a pH in the normal skin pH range, which is between 4.5-6.5. This is because the preparation's pH corresponds to the skin's pH range; besides that, the dispersion and homogeneity that meets the requirements can disperse the active substance optimally to provide moisture and calm to the skin. The ideal topical preparation is non-irritating to the skin. The possibility of skin irritation will be substantial if the preparation is too acidic or too alkaline (Susilowati et al., 2014). Ermawati et al. (2018) found that the combination of the gelling agents Hydroxy Propyl Methyl Cellulose (HPMC) and Carbopol caused skin reactions or mild irritation; this could be due to the combination of the gelling agents HPMC and Carbopol not being optimized.

CONCLUSION

1. Butterfly pea flower extract (*Clitoria ternatea* L.) can provide inhibition against *Staphylococcus aureus*,

Propionibacterium acnes, and Staphylococcus epidermidis bacteria.

2. The combination of HPMC and Carbomer can affect gel preparations' physical properties when compared to using a single base; the combination of HPMC and Carbomer can form a physically better gel mass, has a high viscosity, good drug release and dissolution, and good bioavailability.
3. 3. The optimum formula for the combination of HPMC and Carbomer using the Simplex Lattice Design method can provide good physical properties such as organoleptic, adhesion, spreadability, pH, and viscosity.
4. 4. The optimum formula of the HPMC and Karbomer gel combination does not irritate because it is in the pH range of normal skin between 4.5-6.5.

THANK-YOU NOTE

Thanks are given to Setia Budi University, specifically to the Pharmacy Masters Study Program,

which always supports this research.

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