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Development of natural rubber latex patch infused with *Piper nigrum* L. extract

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ABSTRACT: *Piper nigrum* L. or black pepper is a well-known spice which is also used in herbal medicine. It has been used as a single herb and in a formula to treat many conditions such as muscle pain. This study develops a transdermal patch using natural rubber latex as a base and infused with *P.nigrum* extract. The physicochemical properties of the prepared patches were optimized with the addition of plasticizers, which are dibutyl phthalate, polyethylene glycol 400 and glycerin. The efficiency of the transdermal patches was evaluated by measuring the releasing profile of piperine, the main active component of *P.nigrum*. Other physical characteristics were measured by the tensile strength, moisture uptake, swelling rate and erosion rate. In conclusion, the formulation with the additives of dibutyl phthalate and glycerin showed good piperine release profile and mechanical properties.

KEYWORDS: Transdermal patch; *Piper nigrum* L.; black pepper extract; natural rubber latex; plasticizer

1. INTRODUCTION

Muscle pain is a common condition found in people of every age. It can be short term such as muscle soreness or injury from exercise and sports activities. For short term pain in working class people, there is a condition known as office syndrome which is caused by incorrect posture and inappropriate repetitive actions that occur in their working area. Muscle pain is also found in chronic conditions such chronic myofascial pain and in some autoimmune diseases such as multiple sclerosis. It is a disturbing condition that affects the quality of life of many people[1]. Chronic pain is categorized as a persisting pain for up to 12 weeks which exceeds the typical recovery time of regular or acute pain. It is found that the prevalence of chronic pain in adults is about 20%. Chronic pain treatment varies with the condition of the person, some might require additional rest or inactivity to improve the recovery while others might require long term analgesic medication to control the severity of the pain. Chronic pain can have a negative impact on many aspects of a person life such as mobility, mental health, sleeping pattern and financial[2].

Black pepper or *Piper nigrum* L. is a well-known medicinal plant listed in many traditional medicines such as Thai Traditional Medicine, Ayurveda, and Traditional Chinese Medicine. It is also a well-known spice used in cuisines all over the world. In term of pharmacological properties, black pepper is report to have activities such as antimicrobial, antioxidant, anticancer, analgesic, anticonvulsant, anti-inflammatory, hypoglycemic, hypolipidemic and neuroprotective[3]. Black pepper is produced from the unripen fruit of *P.nigrum* while white pepper is produced from the ripe fruit. White pepper is also used to treat many conditions in traditional medicine as well. In traditional medicine, black pepper is used to help increase the effect of other medicinal plants and there are studies showing the enhanced bioavailability of conventional medicines such as tetracycline, rifampin, and phenytoin[4]. A herbal formulation of turmeric, black pepper, and ginger showed to have similar efficacy in decreasing prostaglandin E_2 compared to naproxen in patients with chronic knee osteoarthritis over a course of a 4 week treatment[5]. Black pepper can be considered a valuable resource and a potential candidate as a raw material for treatment interventions for analgesic purposes.

In Thai Traditional Medicine, there are many means of treatment for treating muscle pain. Thai traditional massage in combination with herbal compress ball is among the most popular and effective treatment. It is a well-tolerated manual treatment and popular in many countries around the world.

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Moreover, there are also many Thai traditional formulae used for muscle pain treatment as listed in the Thai National List of Essential Medicine there are 6 internal formulae and 2 external formulae[6]. *P.nigrum* is used in many of these formulae. For example, the Sahasthara formula is one of the commonly use Thai traditional herbal formula which consist of 21 medicinal plants and has black pepper as the main ingredient. The formula is shown to have good antioxidant and anti-inflammatory property which corresponds with its traditional indication[7]. Recent study in 62 volunteers demonstrated that a treatment of 1,200 mg/day of Sahasthara for 7 days is comparable to 75 mg/day of diclofenac for 7 days in relieving muscle pain[8]. Moreover, black pepper has been used as an ingredient in topical formulation in many studies, such as topical emulgel for antiaging[9], topical preparation for catheter insertion success[10], and film forming transdermal delivery formulation[11].

P.nigrum is shown to have good potential in both food and medicinal purposes. Chemical constituent of *P.nigrum* revealed piperine as the main active component which reported a content amount of up to 97%. Piperine or 1-piperoylpiperidine is found in other related piper species such as *P.longum*, *P.crussi*, *P.retrofractum*, and *P.geniculatum*. It is also found in other species such as the dried rhizomes of ginger or *Zingiber officinalis*. Piperine is a weak basic alkaloid with a lipophilic character which has low bioavailability due to the limitation in dissolving in water[12]. Previous studies shown that piperine is involved in the digestion enhancement and increase in bioavailability of some drugs. It is also suggested that piperine play an important role in the other bioliogical properties of *P.nigrum* such as antiinflammatory, antibacterial, and antiviral[4].

Transdermal patches are a type of medical device that facilitates drug delivery through the skin. There are records of the use of transdermal delivery since ancient China around 2000BC. They used natural gum rubber as the base which is dispersed with the herbal material and line in on to paper or fabric to create medicated plasters[13]. The first and still available transdermal patch was approved by the USFDA in 1979. It is designed to deliver scopolamine over a course of 3 days for the treatment of motion sickness[14]. According to their design, the transdermal patches can attach on to the skin and prolong or controlled the release of the drug into the skin depending on its formulation[15]. Transdermal patches for pharmaceutical use can be categorized into the matrix (drug-in-adhesive) system and the reservoir, or membrane controlled system[16]. Therefore, they can provide convenience in cases that require multiple drug doses or need a long treatment.

This study develops a transdermal patch by using natural rubber latex (NRL) from rubber trees or *Hevea brasiliensis* (Willd. ex A.Juss.) Müll.Arg. Due to the abundance of NRL in Thailand, finding a novel way to increase its value is of both scientific and public interest. The developed NRL patch is infused with *P.nigrum* extract, which is an important Thai medicinal plant used extensively in both traditional and conventional medicine. The formulation of the patch will be optimized to have optimal physicochemical properties. The NRL patch infused with *P.nigrum* extract can used as an alternative topical treatment for muscle pain but would requires further clinical studies in the future.

2. RESULTS

2.1. Patch preparation

The NRL patches were prepared according to the formulations listed in Table 1. The *P.nigrum* L. extract (PNE) extract was used at 0.5%. There were 2 concentrations of the dry rubber content (DRC), which are DRC of 32% (N30) and 61% (N60), of the NRL used in this study. Plasticizer of dibutyl phthalate (DBP) at a concentration of 10 phr was used in all the designated formula to ensure a strong patch once it is fully polymerized. The PNE was prepared as a stock solution by dissolving 2 g of PNE in 200 ml of 20% ethanol solution, to achieve a concentration of 10 mg/ml based on the dry weight of the PNE. Additional plasticizers which are polyethylene glycol 400 (PEG) and glycerin (GLY), at a concentration of 1 phr, were used as a factor to investigate its effect on the physicochemical property of the developed patches. All the formulation produced a strong and fully polymerized patch after the 3 hours drying process in the hot air oven, except for the N30+DBP+GLY. The latter formulation produced a stretchable patch with very high elasticity but ripped very easily which could not be used in the further evaluation processes.

2.2. Piperine releasing study

The release of the piperine from each formulation was measured in triplicate and results were calculated as ppm of the piperine released in the buffer solution (Figure 1). The amount of piperine was released very quickly as a “burst release” during 0-20 mins. After that during 20-420 mins there was a slower release or a “stable profile”. At the end of the measurement, the formulations that had the amount of

piperine released from highest to lowest was the N30+DBP at 3.51 mg (42.5% of piperine released from the patch), N30+DBP+PEG at 3.45 mg (41.6% of piperine released from the patch, N60+DBP+GLY at 2.70 mg (17.4% of piperine released from the patch), N60+DBP at 1.99 mg (12.8% of piperine released from the patch) and N60+DBP+PEG at 1.80 mg (11.6% of piperine released from the patch), respectively.

2.3. Mechanical property study

The prepared patches were cut in to strips of 10 x 100 mm and the measurement was carried out in triplicate. The higher concentration of the DRC produces a stronger patch as seen in the higher Young's modulus value. This can be seen in the N30+DBP which had the lowest Young's modulus value. The formulation with low DRC with the addition of an additional plasticizer of PEG, N30+DBP+PEG, produced a stronger patch. The formulation with high DRC with the addition of an additional plasticizer of both GLY and PEG, produced a slightly more flexible patch. All data is shown in Table 2.

Table 1. Component of each NRL patch formulations per 1 petri dish

Formulation	NRL (g)	PNE (g)	DBP (g)	PEG (g)	GLY (g)
N30+DBP	1.9	0.08	0.2	-	-
N60+DBP	3.1	0.15	0.4	-	-
N30+DBP+PEG	1.9	0.08	0.2	0.03	-
N60+DBP+PEG	3.1	0.15	0.4	0.04	-
N30+DBP+GLY	1.9	0.08	0.2	-	0.03
N60+DBP+GLY	3.1	0.15	0.4	-	0.04

2.4. Moisture uptake, swelling ratio and erosion study

The prepared patches were cut in to strips of 10 x 10 mm and the measurement was carried out in triplicate. The moisture uptake value of all formulations was comparable. The N30+DBP+PEG formulation had the highest moisture uptake of 3.26%. The N60+DBP+GLY formulation had the lowest moisture uptake of 0.56%. The formulations with low DRC showed to have significantly higher swelling ratio compared to others. The N30+DBP+PEG formulation had the highest swelling ratio of 55.90% while the N60+DBP+PEG formulation had the lowest swelling ratio of 2.63%. The erosion of the prepared patches is correlated with the swelling ratio profile. The formulations with low DRC showed to have significantly higher erosion compared to others. The N30+DBP formulation had the highest erosion of 21.68% while the N60+DBP formulation had the lowest erosion of 5.47%. All data is shown in Table 2.

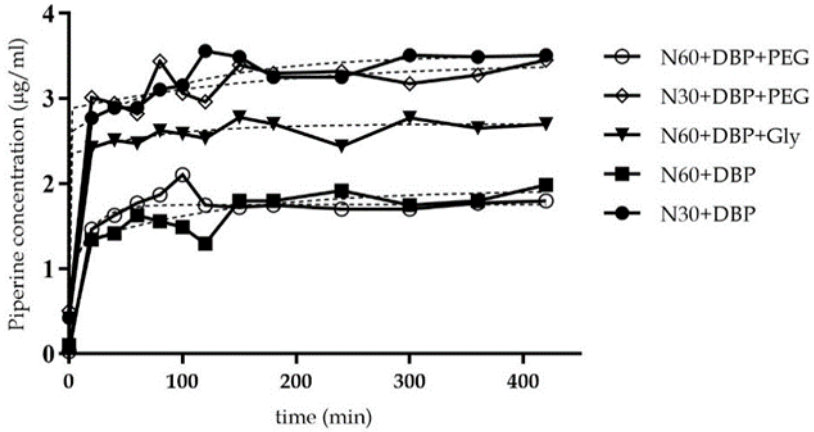

Figure. Piperine releasing profile of each formulation of NRL patch

3. DISCUSSION

The piperine release pattern of the prepared patches all showed to be similar. Starting with an initial burst release and then a stable profile after 20-40 minutes. This active ingredient release characteristic, of a "burst" and "stable" profile, is also reported in other NRL matrix patch experiments with conventional drugs [17][18] and medicinal plant extracts[19]. The amount of piperine release for the N30+DBP and

N30+DBP+PEG was slightly higher when compared to other formulations. The lower concentration of the DRC in the N30 formulations might provide more porous space for water to enter the matrix, hence increases the wettability property as shown in high erosion ratio in Table 2. Although patches with high erosion ratio often have high elasticity, the addition of PEG in N30+DBP+PEG showed to increase the tensile strength. The N30+DBP+PEG also had the highest moisture uptake value, this may be due to the high porous space from the low DRC concentration and the presence of hydrophilic plasticizer, PEG. Notably, the N60+DBP+GLY formulation showed to be able to release piperine higher than the other formulation with high DRC concentration, N60. It also did not have a high erosion property. This increase in piperine release might be due to the increase of hydrophilicity from the addition of glycerin, which is similar to results in previous studies[20].

Table 2. Calculated Young's Modulus, moisture uptake, swelling ratio and erosion ratio

Formulation	Young modulus (MPa)	Moisture uptake (%)	Swelling ratio (%)	Erosion (%)
N30+DBP	3.4 ± 0.8	1.63 ± 0.02	42.88 ± 4.10	21.68 ± 1.02
N60+DBP	29.0 ± 4.2	2.64 ± 0.03	5.53 ± 0.36	5.47 ± 0.34
N30+DBP+PEG	25.1 ± 1.8	3.26 ± 0.05	55.90 ± 6.41	17.92 ± 1.86
N60+DBP+PEG	19.9 ± 1.2	1.66 ± 0.01	2.63 ± 0.10	6.21 ± 0.95
N60+DBP+GLY	21.1 ± 0.1	0.56 ± 0.01	6.87 ± 0.42	6.84 ± 0.84

The piperine releasing profile (**Figure**) show similar release as biexponential function compared to similar studies on NRL[21]. This can be seen in the expression of $y(t) = y0 + A1e(-t/\tau1) + A2e(-t/\tau2)$, where $y(t)$ is the amount of compound in the NRL at a given time, t, $y0$ is the initial content, and $A1$, $A2$, $\tau2$, and $\tau2$ are constants. The "burst release" may be due to the piperine which is located on the surface of the patch, and the slower release or the "stable profile" may be due to the gradual diffusion of piperine from the membrane reservoir. This can occur through the membrane pores and fractures from the erosion of the membrane. The plateau phase or saturation is reached at approximately 40 minutes. The parameters for the biexponential exponential best fit are shown in Table 3.

Polyethylene glycol 400 has high hydrophilicity and during the preparation, it can induce the polymerization process of the NRL very fast. This ability might be the reason for the increase in tensile strength of the N30+DBP+PEG when compared to N30+DBP. But in the case of the N60 formulations, the addition of PEG seems to increase the elasticity of the N60+DBP+PEG formulation when compared to N60+DBP.

In terms of adhesive properties, all the formulations shown to have low skin adhesive properties. An additional adhesive which is safe for use on the skin may need to be added to the prepared patches to be an appropriate application

From the results, it demonstrates that using a low concentration NRL will produce a patch with low strength, high elasticity, and high swelling rate. Conversely, using a high concentration NRL will produce a patch with higher strength, lower elasticity, and lower swelling rate. Therefore, a higher concentration would be more favorable in producing durable transdermal patch. The addition of the plasticizer has helped improve the properties of the patches, which did not have much impact on the release of piperine from the patches. These results suggest that NRL is a good material for the construction of transdermal patches for the use of drug delivery or other medical purposes in the future. However, further clinical studies are required prior to the commercialization of these developed NRL patches infused with active pharmaceutical ingredients or medical plant extracts. In economical perspectives, there is a high supply of NRL in many countries, especially in Thailand. This can ensure the continuous production of the NRL transdermal patch which can help increase the value of this valuable natural resource as well.

4. CONCLUSION

NRL can polymerize and be formed into patches which have high tensile strength but with low elasticity and low skin adhesive properties. The addition of the plasticizers in all the formulations improved the elasticity of the prepared patch. The formulation which used NRL with 61% DRC with the plasticizers of DBP and glycerin shown to be the best patch in terms of good piperine release profile and good mechanical properties. This indicates that the prepared NRL patch blended with plasticizer of DBP with glycerin is a good candidate for further development of a transdermal patch with PNE or other herbal formula extract.

Table 3. Parameters for fitted bi-exponential equation of piperine release of each formulation

Formula	$y0$	$A1$	$A2$	$\tau1$	$\tau2$
N30+DBP	0.043	0.92	2.16	0.0060	3.24
N60+DBP	0.093	0.67	1.15	0.0061	56.99
N30+DBP+PEG	0.055	0.55	2.37	0.0060	0.34
N60+DBP+PEG	0.081	0.98	0.74	0.0024	0.19
N60+DBP+GLY	0.068	0.37	1.92	0.0013	70.49

5. MATERIAL AND METHODS

5.1. Material

NRL produced from Hevea brasiliensis (Willd. ex A.Juss.) Müll.Arg clone RRIM 600 was purchased from a local plantation in Phan District, Chiangrai Province, Thailand. Black pepper or *P.nigrum* was purchased from a local herb vendor in Muang District, Chiangrai Province, Thailand.

5.2. Chemicals

Pepper extract (Piperine 98%) was purchased from Chanjao Longevity (Thailand). Dibutyl phthalate (DBP), polyethylene glycol 400 (PEG) and glycerin (GLY) were purchased from Sigma Aldrich (USA). All other chemicals were of commercial grade.

5.3. *P. nigrum* extract preparation

100 g of black pepper was grinded into powder and macerated in 500 ml of 95% ethanol for 24 hours. This process was repeated 3 times and pooled together. The ethanolic solution was then filtered. The filtrate was reduced under vacuum until dry to obtain the PNE of 9.7 g. The PNE was kept in a tight container and refrigerated until further use.

5.4. Patch preparation

The dry rubber content (DRC) of the NRL was determined[22]. The 2 types of the NRL had DRC of 32% (N30) and 61% (N60). The NRL was mixed with the plasticizer and the PNE in different ratios, as shown in Table 1. The mixture was stirred with a homogenizer to ensure proper mixing before pouring into a 100 mm diameter glass petri dish. The dishes were dried in a hot air oven at 60 ± 5 °C for 3 hours. The fully polymerized NRL patches were transferred onto a plastic sheet and kept in an airtight container for further evaluation.

5.5. Piperine releasing study

Piperine is a main component of the PNE, therefore it is used as an indicator to measure the amount of PNE release from the NRL patches. Phosphate buffer solution (PBS) was prepared and pH adjusted to 7.4. The NRL patches were placed in 1,000 ml of PBS and the aliquots of 5 ml were collected at 0, 20, 40, 60, 80, 100, 120, 150, 180, 240, 300, 360 and 420 minutes. PBS at a volume of 5 ml was added after each aliquot to maintain the total volume throughout the study. The piperine content in the extract and the buffer solution was measured by the UV–Vis spectra with a BEL ENGINEERING SF200 ADV spectrophotometer, at maximum absorption at 344 nm. The experiments were carried out in triplicate.

5.6. Mechanical property study

The tensile strength of the NRL patch was expressed as the Young's modulus. The test was carried out with the Instron-5566 Universal Testing Machine (UTM), with a 50 kg load cell at a speed of 100 mm/min and stretched until failure [23]. The Young's modulus was calculated from the stress-strain curve from the initial linear part (0-5% elongation)

5.7. Moisture uptake, swelling ratio and erosion study

The NRL patches were cut into 10 mm x 10 mm and placed in a tight container with silica gel beads for beads for 24 hours. The initial weight (W_0) was collected, and the strips were moved into a tight container with saturated sodium chloride with 75% relative humidity (RH). The strips were removed every week and the weight was recorded until it became constant (W_u). The moisture uptake percentage was calculated by the increased weight ($W_u - W_0$) in comparison to the initial weight (W_0). The swelling ratio and erosion were studied by drying a 10 mm x 10 mm strip of NRL patch at 60 ± 5 °C overnight. The dried strip was weighed (W_0) and then immersed in 5 ml of distilled water at room temperature for 48 hours[23]. Once saturated with water, the strip is removed and weighed (W_s). Then the strips were dried again at 60 ± 5 °C overnight and weighed again (W_d). The swelling ratio was calculated by the increased weight ($W_s - W_0$) in comparison with the initial weight (W_0). The erosion percentage was calculated by the loss of weight ($W_0 - W_d$) in comparison with the initial weight (W_0).

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REFERENCES

[1] Liew BXW, Del Vecchio A, Falla D. The influence of musculoskeletal pain disorders on muscle synergies—A systematic review. PLoS One. 2018; 13(11): e0206885. https://doi.org/10.1371/journal.pone.0206885

[2] Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA, Smith BA. Physical activity and exercise for chronic pain in adults: An overview of Cochrane reviews. Cochrane Database Syst Rev. 2017; 4(4): CD011279. https://doi.org/10.1002/14651858.CD011279.pub3

[3] Takooree H, Aumeeruddy MZ, Rengasamy KRR, Venugopala KN, Jeewon R, Zengin G, Mahomoodally MF. A systematic review on black pepper (*Piper nigrum* L .): From folk uses to pharmacological applications. Crit Rev Food Sci Nutr. 2019; 59: 210–243. https://doi.org/10.1080/10408398.2019.1565489

[4] Meghwal M, Goswami TK. *Piper nigrum* and piperine: An update. Phyther Res. 2013;27(8):1121–1130. https://doi.org/10.1002/ptr.4972

[5] Heidari-Beni M, Moravejolahkami AR, Gorgian P, Askari G, Tarrahi MJ, Bahreini-Esfahani N. Herbal formulation "turmeric extract, black pepper, and ginger" versus Naproxen for chronic knee osteoarthritis: A randomized, double-blind, controlled clinical trial. Phyther Res. 2020; 34(8): 2067–2073. https://doi.org/10.1002/ptr.6671

[6] Ministry of Public Health NDI. National List of Essential Medicine. Government Gazettes. 2018 http://ndi.fda.moph.go.th/uploads/main_drug_file/20180529192247.pdf (accessed on 2 February 2023)

[7] Kakatum N, Jaiarree N, Makchucit S, Itharat A. Antioxidant and anti-inflammatory activities of Thai medicinal plants in Sahasthara remedy for muscle pain treatment. J Med Assoc Thai. 2012; 95(1): 120–126.

[8] Nootim P, Bunchuailua W, Kapol N. Comparative Efficacy of Sahasthara Capsule vs Diclofenac tablet for the relief of muscle pain. J Thai Tradit Altern Med. 2013; 11(1): 54–65.

[9] Yousuf M, Khan HMS, Rasool F, Khan K ur R, Usman F, Ghalloo BA, Umair M, Babalghith AO, Kamran M, Aadil RM, Al Jaouni SK, Selim S, Korma SA, Conte-Junior CA. Chemical profiling, formulation development, ın vitro evaluation and molecular docking of *Piper nigrum* seeds extract loaded emulgel for anti-aging. Molecules. 2022; 27(18):5990. https://doi.org/10.3390/molecules27185990

[10] Eren H, Turkmen AS, Aslan A. Effect of topical application of black pepper essential oil on peripheral intravenous catheter insertion: A randomized controlled study. Explore. 2022; 18(4): 457–462. https://doi.org/10.1016/j.explore.2021.06.001

[11] Asasutjarit R, Sookdee P, Veeranondha S, Fuongfuchat A, Itharat A. Application of film-forming solution as a transdermal delivery system of piperine-rich herbal mixture extract for anti-inflammation. Heliyon. 2020; 6(6) :e04139. https://doi.org/10.1016/j.heliyon.2020.e04139

[12] Quijia CR, Araujo VH, Chorilli M. Piperine: Chemical, biological and nanotechnological applications. Acta Pharm.

2021; 71(2): 185–213. https://doi.org/10.2478/acph-2021-0015

[13] Chien YW. Development of transdermal drug delivery systems. Drug Dev Ind Pharm. 1987; 13(4–5): 589–651. https://doi.org/10.3109/03639048709105212

[14] Pastore MN, Kalia YN, Horstmann M, Roberts MS. Transdermal patches: history, development and pharmacology. Br J Pharmacol. 2015; 172(9): 2179–2209. https://doi.org/10.1111/bph.13059

[15] Floriano JF, de Barros NR, Cinman JLF, da Silva RG, Loffredo AV, Borges FA, Norberto AMQ, Chagas ALD, Garms BC, de Oliveira Graeff CF, Herculano RD. Ketoprofen loaded in natural rubber latex transdermal patch for tendinitis treatment. J Polym Environ. 2018; 26(6): 2281–2289. https://doi.org/10.1007/s10924-017-1127-x

[16] Prodduturi S, Sadrieh N, Wokovich AM, Doub WH, Westenberger BJ, Buhse L. Transdermal delivery of fentanyl from matrix and reservoir systems: Effect of heat and compromised skin. J Pharm Sci. 2010; 99(5): 2357–2366. https://doi.org/10.1002/jps.22004

[17] Morise BT, Chagas ALD, Barros NR, Miranda MCR, Borges FA, Gemeinder JLP, Silva RG, Paulino CG, Herculano RD, Norberto AMQ. Scopolamine loaded in natural rubber latex as a future transdermal patch for sialorrhea treatment. Int J Polym Mater Polym Biomater. 2019; 68(13):788–795. https://doi.org/10.1080/00914037.2018.1506984

[18] Yonashiro Marcelino M, Azevedo Borges F, Martins Costa AF, De Lacorte Singulani J, Ribeiro NV, Barcelos Costa-Orlandi C, Garms BC, Soares Mendes-Giannini MJ, Herculano RD, Fusco-Almeida AM. Antifungal activity of fluconazole-loaded natural rubber latex against *Candida albicans*. Future Microbiol. 2018;13(3):359–367. https://doi.org/10.2217/fmb-2017-0154

[19] Romeira MK, Drago BC, Murbach HD, Aielo BP,da Silva MGR, Brunello AC, Hercula DR. Evaluation of Stryphnodendron sp. release using natural rubber latex membrane as carrier. J Appl Sci. 2012; 12(7): 693–697. https://doi.org/10.3923/jas.2012.693.697

[20] Pichayakorn W, Suksaeree J, Boonme P, Amnuaikit T, Taweepreda W, Ritthidej GC. Deproteinized natural rubber latex/hydroxypropylmethyl cellulose blending polymers for nicotine matrix films. Ind Eng Chem Res. 2012; 51(25): 8442–8452. https://doi.org/10.1021/ie300608j

[21] Azevedo Borges F, Cesar Bolognesi LF, Trecco A, de Camargo Drago B, Baldo de Arruda L, Noronha Lisboa Filho P, Gonçalves Pierri E, de Oliveira Graeff CF, Gonzaga dos Santos A, Romeiro Miranda MC, Donizetti Herculano R. Natural rubber latex: Study of a novel carrier for *Casearia sylvestris* Swartz delivery . ISRN Polym Sci. 2014; Article ID 241297. https://doi.org/10.1155/2014/241297

[22] Hamza ZP, Dilfi KFA, Muralidharan MN, Kurian T. Microwave oven for the rapid determination of total solids content of natural rubber latex. Int J Polym Mater Polym Biomater. 2008; 57(9): 918–923. https://doi.org/10.1080/00914030802153066.

[23] Pichayakorn W, Suksaeree J, Boonme P, Amnuaikit T, Taweepreda W, Ritthidej GC. Nicotine transdermal patches using polymeric natural rubber as the matrix controlling system: Effect of polymer and plasticizer blends. J Memb Sci. 2012; 411–412: 81–90. https://doi.org/10.1016/j.memsci.2012.04.017