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EFFECTS OF TRANSDERMAL DOSAGE FORMS ON *IN VITRO* PIG SKIN PERMEATION
OF GLUCOSAMINE HYDROCHLORIDE

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A Thesis Submitted in Partial Fulfillment of the Requirements
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กลูโคซามีนไฮโดรคลอไรด์ ซึ่งเป็นสารในกลุ่มอะมิโนโมโนแซคคาไรด์ที่สามารถพบในร่างกายมนุษย์ จัดเป็นยาบรรเทาอาการในโรคข้อเสื่อม การศึกษาผลของรูปแบบยาผ่านผิวหนังและส่วนประกอบของตำรับที่มีต่อการซึมผ่านผิวหนังแบบนอกกายของตัวยา ทำโดยใช้ชุดฟรานซ์ดีฟิวชันเซลล์ ที่อุณหภูมิ 32 องศาเซลเซียส ในระยะเวลา 24 ชั่วโมง การวิเคราะห์หาปริมาณตัวยากลูโคซามีนไฮโดรคลอไรด์ใช้วิธีวิเคราะห์ด้วยโครมาโตกราฟีชนิดของเหลวสมรรถนะสูง โดยทำปฏิกิริยาระหว่างกลูโคซามีนไฮโดรคลอไรด์กับสารฟีนิลไอโซไซยาเนตก่อนทำการวิเคราะห์ ทำการคำนวณหาค่าร้อยละของปริมาณสะสมของยาที่ซึมผ่านผิวหนังที่เวลา 24 ชั่วโมงและค่าคงที่ของการซึมผ่านผิวหนัง ในช่วงเวลา 6 ชั่วโมง ของสูตรตำรับที่ใช้ได้แก่สารละลายน้ำ สารละลายไฮโดรแอลกอฮอล์ เจลและไมโครอิมัลชันที่ความเข้มข้นของตัวยาร้อยละ 2 พบว่าสูตรตำรับที่มีประสิทธิภาพในการช่วยการซึมผ่านของยาเข้าสู่ผิวหนังมากที่สุดเรียงตามลำดับ ได้แก่ ไมโครอิมัลชันที่เตรียมจากทวิน 80 (ปริมาณสะสมของยาที่ซึมผ่านผิวหนังเท่ากับ 47.78% ค่าคงที่ของการซึมผ่านผิวหนังเท่ากับ 9.6×10^{-5} เซนติเมตรต่อวินาที) สารละลายไฮโดรแอลกอฮอล์ที่ความเข้มข้นของเอทานอลเท่ากับร้อยละ 10 (ปริมาณสะสมของยาที่ซึมผ่านผิวหนังเท่ากับ 38.05% ค่าคงที่ของการซึมผ่านผิวหนังเท่ากับ 7.0×10^{-5} เซนติเมตรต่อวินาที) สารละลายน้ำ (ปริมาณสะสมของยาที่ซึมผ่านผิวหนังเท่ากับ 34.04% ค่าคงที่ของการซึมผ่านผิวหนังเท่ากับ 6.4×10^{-5} เซนติเมตรต่อวินาที) เจลที่เตรียมจากเซพิเอ็มซี (ปริมาณสะสมของยาที่ซึมผ่านผิวหนังเท่ากับ 27.63% ค่าคงที่ของการซึมผ่านผิวหนังเท่ากับ 6.0×10^{-5} เซนติเมตรต่อวินาที) ไมโครอิมัลชันที่เตรียมจากเซทิลไตรเมทิลแอมโมเนียมโบรไมด์ (ปริมาณสะสมของยาที่ซึมผ่านผิวหนังเท่ากับ 20.11% ค่าคงที่ของการซึมผ่านผิวหนังเท่ากับ 3.8×10^{-5} เซนติเมตรต่อวินาที) ไมโครอิมัลชันที่เตรียมจากโซเดียมบิสทุเอทิลเฮกซิลซิลไฟซ์ซินเนต (ปริมาณสะสมของยาที่ซึมผ่านผิวหนังเท่ากับ 19.87% ค่าคงที่ของการซึมผ่านผิวหนังเท่ากับ 0.99×10^{-5} เซนติเมตรต่อวินาที) ไมโครอิมัลชันที่เตรียมจากเลซิทีน (ปริมาณสะสมของยาที่ซึมผ่านผิวหนังเท่ากับ 0.83% ค่าคงที่ของการซึมผ่านผิวหนังเท่ากับ 0.21×10^{-5} เซนติเมตรต่อวินาที) พบว่าปริมาณการซึมผ่านของยาเข้าสู่ผิวหนังมีแนวโน้มที่จะคงที่ภายหลังเวลาผ่านไป 6 ชั่วโมง ในสารละลายไฮโดรแอลกอฮอล์ที่มีเอทานอลปริมาณน้อยสามารถช่วยเพิ่มการซึมผ่านของยาสู่ผิวหนังได้ แต่ผลการซึมผ่านเข้าสู่ผิวหนังของยาจะมีค่าลดลงเมื่อมีเอทานอลปริมาณมากเนื่องจากผลการทำลายโปรตีนที่อยู่ในผิวหนัง การซึมผ่านของตัวยากรบบไมโครอิมัลชันที่เตรียมจากทวิน 80 ชนิดน้ำมันในน้ำให้ประสิทธิภาพการซึมผ่านของยาเข้าสู่ผิวหนังได้ดีที่สุด จากผลการทดลองพบว่ามีความเป็นไปได้ที่จะนำส่งยาไกลูโคซามีนไฮโดรคลอไรด์ผ่านทางผิวหนัง อย่างไรก็ตามผลของรูปแบบยาต่อการซึมผ่านทางผิวหนังมนุษย์ควรต้องมีการศึกษาอย่างละเอียดต่อไป

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ลายมือชื่อผู้ผลิต.....พัลลภา อนุสิษฐกุล.....
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PUNLAPA ANUSITTHAKUL : EFFECTS OF TRANSDERMAL DOSAGE FORMS ON *IN VITRO* PIG SKIN PERMEATION OF GLUCOSAMINE HYDROCHLORIDE. THESIS ADVISOR : PHANPHEN WATTANAARSAKIT Ph.D., THESIS COADVISOR : JITTIMA CHATCHAWALSAISIN Ph.D., 133 pp.

Glucosamine hydrochloride (GS HCl), the aminomonosaccharide present in the human body, is classified as symptom modifying drug in osteoarthritis disease. The effects of transdermal dosage forms and their components on permeation of the GS HCl through pig ear skin *in vitro* were elucidated using Franz-diffusion cells at 32°C for 24 hours. The GS HCl was determined quantitatively using validated HPLC method by pre-column with phenylisothiocyanate (PITC) derivatization. The percent cumulative amount of permeated drug after 24 hours and the permeability constant (k_p) up to 6 hours of various dosage forms, solution, hydroalcoholic solution, gel and microemulsion containing 2% GS HCl was calculated. The potential of enhancing permeability of the dosage forms studied can be ranked as the following, Tween 80 microemulsion (cumulative amount of permeated drug 47.78%, $k_p=9.6 \times 10^{-5}$ cm/s), hydroalcoholic solution contain 10% ethanol (cumulative amount of permeated drug 38.05%, $k_p=7.0 \times 10^{-5}$ cm/s), water solution (cumulative amount of permeated drug 34.04%, $k_p=6.4 \times 10^{-5}$ cm/s), HPMC gel (cumulative amount of permeated drug 27.63%, $k_p=6.0 \times 10^{-5}$ cm/s), cethyltrimethylammonium bromide microemulsion (cumulative amount of permeated drug 20.11%, $k_p=3.8 \times 10^{-5}$ cm/s), sodium bis (2-ethylhexyl) sulfosuccinate microemulsion (cumulative amount of permeated drug 19.87%, $k_p=0.99 \times 10^{-5}$ cm/s) and lecithin microemulsion (cumulative amount of permeated drug 0.83%, $k_p=0.21 \times 10^{-5}$ cm/s). The permeation tended to reach a plateau after 6 h. The presence of small quantity of ethanol in hydroalcoholic solution could enhance the drug permeability but with high content of ethanol failed to enhance the drug permeation as a result of protein denaturation in pig skin. Tween 80 microemulsion whereby its type has to be oil in water could effectively enhance the permeability of GS HCl. The results indicate that there is a possibility to develop a GS HCl. transdermal dosage forms. However, the effect of the dosage forms on the drug permeation through human skin needs to be further refined.

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LIST OF ABBREVIATIONS

| | | |
|---------------|---|--|
| AOT | = | sodium bis (2-ethylhexyl) sulfosuccinate |
| ° c | = | degree Celsius |
| cm | = | centimeter |
| CTAB | = | cetyltrimethylammonium bromide |
| et al | = | et alii , ' and others' |
| g | = | gram |
| GS HCl | = | glucosamine hydrochloride |
| h | = | hour |
| HPMC | = | hydroxypropyl methylcellulose |
| IPM | = | isopropyl myristate |
| kg | = | kilogram |
| k_p | = | permeability constant |
| μg | = | microgram |
| μl | = | microliter |
| LM | = | light microscopy |
| ME | = | microemulsion |
| mg | = | milligram |
| min | = | minute |
| ml | = | milliliter |
| nm | = | nanometer |
| PBS | = | phosphate buffer saline |
| PC | = | phosphatidylcholine |
| PITC | = | phenyl isothiocyanate |
| pH | = | the negative logarithm of the hydrogen concentration |
| SE | = | standard error |
| s | = | second |
| v / v | = | volume by volume |
| w / w | = | weight by weight |