An Investigation on the Naproxen Solubility and Permeability Enhancement in Poly (Vinyl Alcohol) Gel for Topical Application

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Abstract—The objective of this research is to evaluate the influence of nano-suspension technique and cyclodextrin inclusion technique on the solubility and in vitro diffusion characteristics of Naproxen in Poly(vinyl alcohol) gel. It is found that combination of both techniques is recommended for future work in order to obtain the best improvement in solubility, anti-trypsic activity and permeability of Naproxen.

Keywords—Naproxen, Solubility, Permeability, Poly (Vinyl Alcohol) Gel, A. FE-SEM.

I. INTRODUCTION
NAPROXEN is a non-steroidal anti-inflammatory drug (NSAID), with analgesic, antipyretic and anti-inflammatory properties for numerous musculoskeletal disorders. It is normally given orally but it gives many undesirable side effects, mainly gastrointestinal problems, which can be avoided through dermal route. However, the major problem of dermal route is low water solubility of Naproxen, leading to reduced penetration of drug across skin. Thus in this research, nanosuspension technique and cyclodextrin inclusion technique are used to solve the solubility and permeability problems of Naproxen.

II. RESEARCH OBJECTIVES
To evaluate the influence of nano-suspension technique and cyclodextrin inclusion technique on the solubility and in vitro diffusion characteristics of Naproxen in Poly(vinyl alcohol) gel.

III. MATERIALS
Naprosyn® USP gel, Naproxen powder, β-cyclodextrin, polysorbate 80, methanol, ethyl acetate, sodium chloride, disodium hydrogen phosphate, poly(vinyl alcohol) powder, triethanolamine, cellulose nitrate membrane, isopropyl myristate, trypsin, casein enzyme hydrolysate, dimethyl sulphoxide, tris-CL buffer powder and trichloroacetic acid.

IV. METHODS
A. Preparation of nano-suspension
Naproxen was dissolved in ethyl acetate (organic solvent with boiling point of 77°C). Stabilizing surfactant, polysorbate 80 was added to distilled water and solution was heated to 80-85°C. Naproxen in ethyl acetate was transferred to distilled water drop-wise via syringe and mixture was continuously stirred magnetically. Ethyl acetate was allowed to evaporate and nanosuspension formed.

B. Preparation of inclusion complex
β-CD inclusion complex of Naproxen was prepared in molar ratio of 2:1 (β-CD : Naproxen) by kneading technique. β-CD was placed in mortar and wetted with few drops of 1:1 mixture of methanol-water and kneaded with Naproxen by geometry mixing to obtain a mass with pasty consistency. Mixture was allowed to dry and inclusion complex formed.

C. Particle size studies for nanosuspension
Studies were done by field emission scanning electron microscope (FE-SEM).

D. Drug content analysis
Samples were dissolved in methanol and mixture was filtered and diluted. Absorbance was measured by UV-VIS spectrophotometer at 262nm.

E. Solubility studies
Samples which contain equivalent amount of Naproxen were dissolved in distilled water. Then, all samples were placed in shaker for 30 minutes. Next, samples were centrifuged at 4000rpm at 25°C for 20 minutes. Lastly, absorbance of supernatant was measured by UV-VIS spectrophotometer at 262nm.
F. Determination of anti-tryptic activity

0.06 ml of trypsin, 0.94ml of 25 Mm tris-Cl buffer and 1ml of sample were added and incubated at 37°C for 5 minutes. Then, 1 ml of 0.8% (w/v) casein was added and mixture incubated for 20 minutes. Next, 2ml of Trichloro acetic acid was added to terminate the reactions. Samples centrifuged at 2000rpm at 25°C for 20 minutes. Percentage of anti-tryptic activity was calculated. [15]

G. In vitro permeation studies

In vitro permeation studies were done by Franz diffusion cells. Temperature of the diffusion medium (water) was maintained at 32oC. Phosphate-buffered saline (pH7.4) was used as receptor fluid. Cellulose nitrate membrane filters (0.1-µm pore diameter) was soaked in isopropyl myristate to simulate lipophilic stratum corneum and then mounted on diffusion cell. 1g of gel was applied onto the donor compartment. Samples are collected over 6 hours and analyzed by using UV spectrophotometer at 262nm.[14,16]

H. Statistical analysis

SPSS program was used to analysis data obtained. One way ANOVA was used for solubility testing whereas two way ANOVA was used for proteolytic and in vitro permeation studies.

V. RESULTS AND DISCUSSIONS

A. FE-SEM for nanosuspension

From the images, particle size of suspension shown was in micrometer size and crystallization was observed. Ostwald ripening may happened during the preparation which cause crystallization due to particles in the solution.[1,2] Agglomeration of drug particles may lead to increased particle size.

However, sample with same formulations was investigated for several tests and proved to improve the solubility and permeability of Naproxen. This proved that samples undergo size reduction or some modifications which favour its solubility and permeability profile. Some problems suspected during FE-SEM analysis including the conversion of liquid to solid form of sample for analysis which may cause spoilage of sample and freshness of sample for analysis as time may favor crystallization.

B. Drug content analysis

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>DRUG CONTENT ANALYSIS TO DETERMINE PERCENTAGE OF NAPROXEN IN SAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nanosuspension of Naproxen</td>
<td>B-CD inclusion complex of Naproxen</td>
</tr>
<tr>
<td>95.28%</td>
<td>90 %</td>
</tr>
</tbody>
</table>

From figure 2, both techniques showed improvement of water solubility. Cyclodextrin techniques are better than nanosuspension technique and β-cyclodextrin inclusion complex of Naproxen (1:2) showed the highest water solubility, which is approximately 10 times better than plain Naproxen. Cyclodextrin molecule can generate a hydrophilic external surface and non polar internal cavity. Therefore, when drug interacts with cyclodextrin molecule, drug will entrapped inside cyclodextrin cavity to form a stable inclusion.
complex, thereby improving solubility of poorly water soluble drugs. Nanosuspension technique reduces drug particle size, thus increasing drug’s water solubility.

D. Anti-tryptic activity studies

Anti-tryptic activity study was based on enzyme reaction between trypsin (enzyme) and casein (protein). Trypsin breakdown casein and lead to cascade of enzyme reaction which cause inflammation and pain. Naproxen has anti-tryptic activity thus giving anti-inflammatory effect. [15]

From figure 3, nanosuspension showed highest anti-tryptic activity, indicating the strongest anti-inflammatory effect. This may be due to reduced particle size in nanosuspension which increases surface area of Naproxen, leading to a better anti-tryptic activity as there are greater interaction between Naproxen and trypsin. Inclusion complex showed the lowest anti-tryptic activity, this may because of Naproxen being entrapped inside cyclodextrin cavity which makes it unavailable for interaction with trypsin.

E. In vitro permeation studies

From figure 4, nanosuspension gel showed highest permeability, which is about 4 times higher than Inclusion complex showed lower permeability than plain Naproxen because complex formed have bigger size and Naproxen entrapped in the cavity thus reducing its permeability across membrane.

VI. CONCLUSION

Nanosuspension technique significantly improves solubility, anti-tryptic activity and permeability of Naproxen. Cyclodextrin inclusion technique only greatly increase solubility of Naproxen but showed no significance difference in anti-tryptic activity and permeability of Naproxen. In terms of solubility, effect of cyclodextrin inclusion complex is better compared to nanosuspension.

In a nutshell, combination of both techniques is recommended for future work in order to obtain the best improvement in solubility, anti-tryptic activity and permeability of Naproxen.

REFERENCES


