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# ANALYSIS OF TRANSDERMAL GEL FORMULATION OF APREPITANT

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## INTRODUCTION

Chemotherapy induced nausea and vomiting is a major problem that affects cancer patients' quality of life and compliance to treatment regimen. One of the major causes of nausea and vomiting in the cancer patients is drug administration including cytotoxic and opioid analgesics. Its management is a huge burden on medical care and requires the use of rescue medication and emergency admission. Current guidelines propose 5-$HT_3$ receptor antagonists as a pharmacological intervention for acute and delayed chemotherapy induced nausea and vomiting[1]. Aprepitant is a newer antiemetic drug that acts as neurokinin 1 receptor antagonist in the chemoreceptor trigger zone and prevents vomiting in patients undergoing chemotherapy. Combination of aprepitant, a 5-HT-3 receptor antagonist, and dexamethasone prevents acute emesis is administered by intra-venous route, which is invasive and possess less patient compliance. Thus, an alternative route for antiemetic therapy could be more advantageous. The Transdermal Drug Delivery System (TDDS) is a novel route for systemic drug delivery through intact skin. It also ensures that compounds are delivered, preferably at a specific rate to the circulation. Due to low solubility of aprepitant, a gel formulation can be developed. Among the various transdermal delivery systems, topical gel technology is preferred due to its superior efficiency, low irritation, longer duration of action (for once daily dosing) and higher patient satisfaction. Lecithin organogels show very promising results in transdermal drug delivery and they are known to be biocompatible. Optimization of the gel can be done by the addition of gelatin and further cross linking agents. They increase the drug permeation and provide for the slow and steady release of drugs.

## REVIEW OF LITERATURE

Chemotherapy induced nausea and vomiting adversely affects patient health, quality of life and decreases patient's chemotherapy treatment adherence. Current guidelines propose 5-$HT_3$ receptor antagonists as a pharmacological intervention for acute and delayed nausea and vomiting.[1] Aprepitant, a neurokinin 1 receptor antagonist in the CTZ, is an orally available antiemetic indicated for prevention of post-operative or chemotherapy induced nausea and vomiting (Bioavailability = 60-65%). It is made up of a morpholine core with 2 substituents (trifluoromethylated 1-phenyl ethanol and fluorophenyl group) attached to the adjacent ring carbons. Sometimes a 3$^{rd}$ substituent (triazoline) is joined to the morpholine ring Nitrogen. It is an off-white crystalline solid with limited water solubility but high solubility in non-polar molecules like oils. [2]

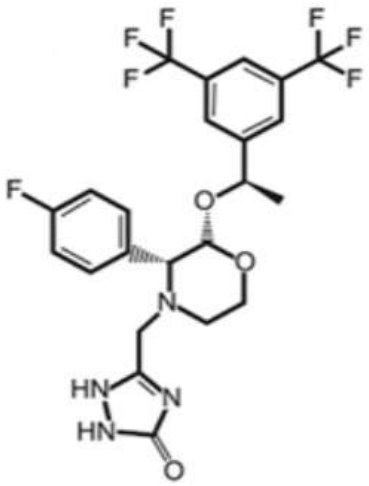


**Figure (1). Chemical structure of Aprepitant**

Combination of aprepitant, a 5-HT-3 receptor antagonist, and dexamethasone prevents acute emesis is administered by intra-venous route, which is invasive and possess less patient compliance. Thus an alternative route for combination antiemetic therapy could be more advantageous. [3] The Transdermal Drug Delivery System (TDDS) is one of the novel routes for systemic delivery of drugs through the intact skin. The ultimate goal of this dosage design is to maximize the flux through skin and at the same time minimize retention and metabolism of drug in the skin. [4] It also ensures that compounds are delivered, preferably at a specific rate, to the systemic circulation. The drug initially penetrates through the stratum corneum and then passes through the deeper epidermis and dermis without drug accumulation in the dermal layer. When drug reaches the dermal layer, it becomes available for systemic absorption via the dermal microcirculation.

It avoids gastrointestinal degradation and hepatic first-pass effect and lends itself to controlled, sustained delivery. It has high adaptability and versatility and is well suited for patients who are unable to take or retain oral medications. Its non-invasive nature is an additional advantage which provides incessant drug delivery to skin similar to intravenous administration, eliminating the vascular access. [5] The pharmacokinetic profiles of drugs are more uniform with fewer peaks, thus minimizing the risk of toxic side effects. [6] It can improve patient compliance due to the reduction of dosing frequencies and is also suitable for patients who are unconscious or vomiting, or those who rely on self-administration. TDDS avoids pre-systemic metabolism, thus improving bioavailability. To be delivered transdermally, an ideal drug should have the following properties: low molecular weight (less than 1000 Da), affinity for lipophilic and hydrophilic phases, low melting point, have a short half-life and non-irritating[7].

Considering the properties of the antiemetic, the feasibility of fabricating transdermal patch was assessed using various pressure sensitive adhesives. Due to its low solubility, it was thought worth to develop a gel formulation as an alternative[3]. Among the various transdermal delivery systems, topical gel technology has gained the attention of drug delivery scientists due to its superior efficiency, low irritation and higher patient satisfaction. the gel system has the capability to deliver the drug over a very long period of time from 12 to 24 h continuously make it suitable for once daily application. [3]

In this perspective, pluronic lecithin organogels could be the most feasible option to incorporate aprepitant in view of its solubility. Pluronic lecithin organogels are extensively used in transdermal formulations as it can incorporate drug molecules with distinct solubility, no skin irritation, potential to disturb the lipid bilayer layer in the stratum corneum, provides rapid permeation etc[8]. Various active and passive methods are explored to optimise the formulation and its delivery. Chemical cross linking agents like glutaraldehyde and glacial acetic acid are incorporated to establish a slow and steady drug release from the gel formulation.

## AIMS AND OBJECTIVES

1. To prepare and optimise a gel formulation containing the antiemetic drug – Aprepitant
2. To design & study the transdermal drug delivery system for the same
3. To study various biopharmaceutical properties including drug release study
4. To compare the effect of 2 different chemical cross linking agents used
5. To determine the stability of the gel formulation

## MATERIALS AND METHODS

**Study design** – Product development and Analysis
**Type of study** – Prospective Analytical study
**Duration of study** – 2 months

## MATERIALS

- Aprepitant
- Lecithin
- Isopropyl myristate
- Sorbic acid
- Poloxamer 407
- Potassium sorbate
- Propylene glycol
- Triton X100
- Ethanol 95%
- Gelatin
- Glacial acetic acid
- Glutaraldehyde

**Figure (2). Using a vortex mixer**

## METHODS

### I. Preparation of gel formulation of Aprepitant :

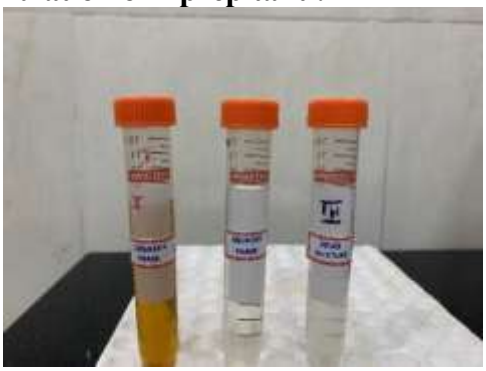

**Figure (3). Preparation of gel formulation from organic and aqueous phase separately**

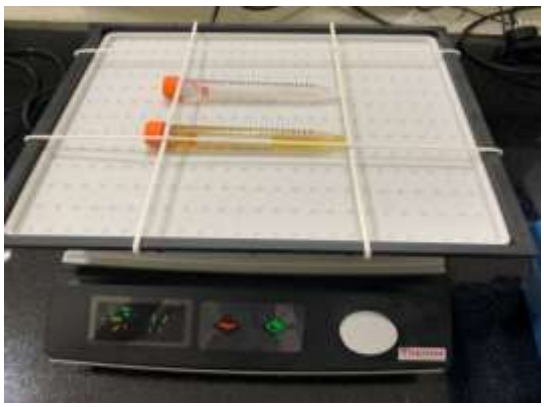

**Figure (4). Rocking shaker**

The gel containing aprepitant was formulated by preparing the organic and aqueous phases separately. The organic phase was prepared by weighing and adding required amount of lecithin and isopropyl myristate (1:1) in a glass vial. To this required amount of sorbic acid (0.2% w/w) was added, mixed and the dispersion was kept overnight for complete dissolution to obtain a homogenous clear solution. Similarly, the aqueous phase was prepared by cold process. The required amount of poloxamer 407 (20% w/v) and potassium sorbate (0.2% w/w) were weighed and added slowly to the cold water with continuous stirring at lower temperature (4-5 °C) until the polymer was uniformly dispersed. The dispersion was refrigerated (4-5 °C) overnight to obtain a homogenous clear solution. Aprepitant was dissolved in mixture of propylene glycol, triton X100 and ethanol (95%) (1:1:4) with continuous stirring and added to the organic phase and mixed using magnetic stirrer to obtain a clear solution. After that the cold aqueous phase (4 parts) was added slowly to the organic phase (1 part) under continuous stirring at low temperature (4-5°C) using homogenizer to obtain gel. [14]

## II. Gel film cross linking & characteristics :


**Figure (5). Dry bath incubator Figure (6). Mini centrifuge Figure (7). Sonicator**

The obtained gel formulation of the drug is taken in little amounts in microcentrifuge tubes and gelatin (10% w/v) is added. Chemical methods of crosslinking are employed. To one set of tubes, optimum amount of glacial acetic acid (20% w/w) is added and to the other set, optimum amount of 25% glutaraldehyde (3% volume) is added. This is subjected to heating in dry bath incubator & stirring using sonicator (figure 7) & mini centrifuge (figure 6). The chemically crosslinked gel formulation was cast in petri dishes as films of area 5cm x 5cm and left overnight and films are formed. The thickness of the gel film was measured using Vernier calipers. The weight of the crosslinked polymer is calculated using electronic weighing apparatus and mean value was calculated.

**Figure (8). Casting the gel film**

## III. In vitro drug release studies :

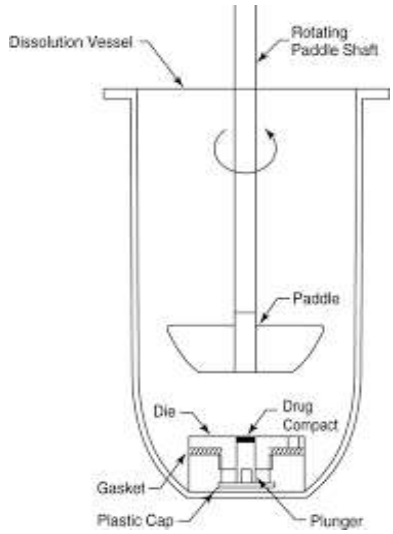


**Figure (9). Rotating Paddle**

The US Pharmacopeia XXIII rotating paddle method was used to study the drug release from the designed transdermal delivery system. The dissolution medium consisted of 250 ml of phosphate buffer solution of pH 6.8. The release was performed at 37±0.5ºC with a rotation speed 50 rpm. The one side of the polymer film was attached to a 3 cm diameter glass disk with instant adhesive (cyanoacrylate adhesive). The film with glass disk was placed at the bottom of the dissolution vessel so that the film dosage form faced upright thereby allowing drug release only from the upper side of the film [17]. Samples of 5ml were withdrawn at pre-determined time intervals and replaced with fresh medium. The samples were filtered through 0.45-µm filter (Millipore Co., Bedford, MA, USA) and analyzed after appropriate dilution by UV spectrophotometry (Jenway 6715, Essex, UK) at λmax 237 nm. The release studies were conducted in triplicates and the mean values were plotted versus time.

## IV. Gel Film Cast :

**Figure (10)**

### V. Folding Endurance :

Folding endurance was determined by repeatedly folding a small strip of film at the same place till it broke. The number of times, the film could be folded at the same place without breaking, gave the value of folding endurance. The results were analyzed for mean and standard deviation.

## OBSERVATIONS AND RESULTS

### In Vitro Drug Release studies:

Drug release was slower from films cross linked with glutaraldehyde than films cross linked with glacial acetic acid. This could have been due to the higher swelling profile and slower erosion rate of glutaraldehyde cross linked films, which created a thick gel barrier, resulting in an increase in diffusional path length of drug and the consequent reduction of drug release [18]. These results were consistent with the literature, in which many authors have generally observed that increasing the amount of hydrophilic polymer in the films produces a water-swollen gel-like state that can substantially reduce the permeation of the dissolution medium into the films and thus retard the drug release [19]. It was obvious that the slowest release was obtained from films cross linked with glutaraldehyde. This could be attributed to the high hydrophobic properties, and the consequent lower dissolution and slower erosion, which prevented free and deep water penetration into the film [20, 21]. The addition of hydrophilic bioadhesive polymers like glutaraldehyde improved the bioadhesion as well as the penetration and release rates of aprepitant, as shown in the figure 11,12 :-

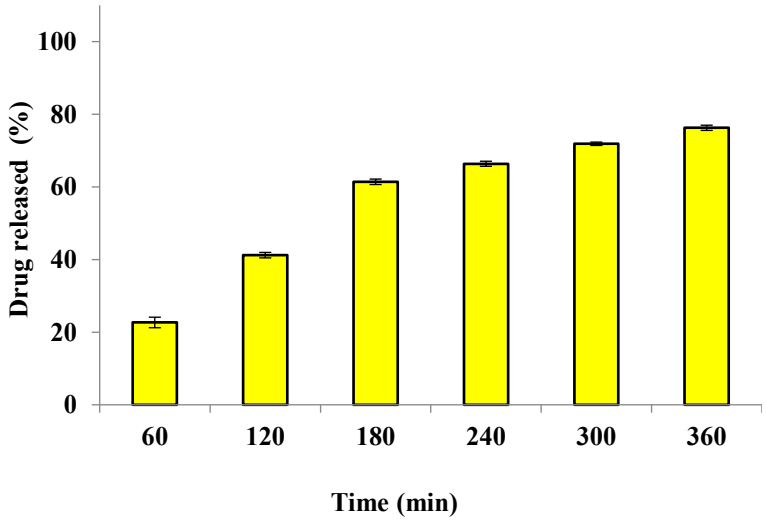


**Figure (11). Drug released by transdermal delivery system cross linked with glutaraldehyde**

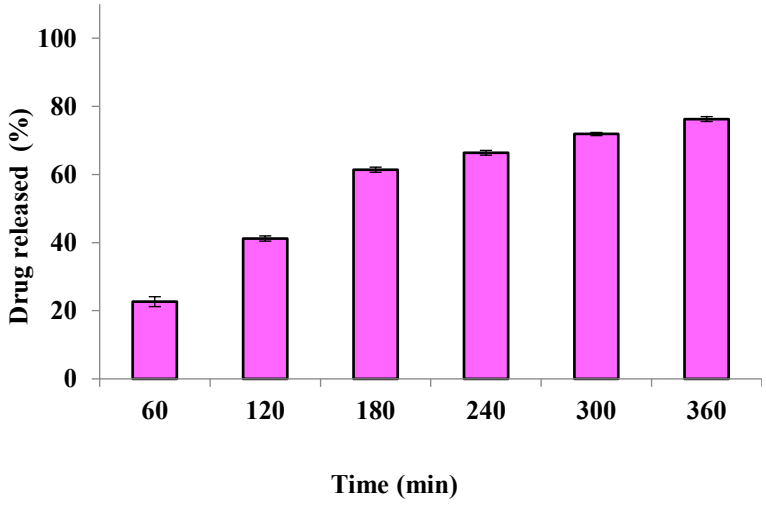


**Figure (12). Drug released by transdermal delivery system cross linked with glacial acetic acid**

**Thickness of film :**
The following table shows the observations from thickness measurement using vernier calipers and the mean values are shown :-

| | 1st (mm) | 2nd (mm) | 3rd (mm) | Mean |
|---|---|---|---|---|
| Glacial Acetic Acid | 0.41 | 0.43 | 0.47 | 0.43 |
| Glutaraldehyde | 1.05 | 1.12 | 1.25 | 1.14 |

**Table (1). Thickness of glacial acetic acid and glutaraldehyde cross linked polymer**

**Weight:**
The following table shows the weight measurments of 5cm X 5cm patches of the cross linked polymer – gel film :-

| | 1st (g) | 2nd (g) | 3rd (g) | Mean (g) |
|---|---|---|---|---|
| Glacial Acetic Acid | 0.07718 | 0.08654 | 0.0912 | 0.08497 |
| Glutaraldehyde | 1.0578 | 2.0567 | 2.12678 | 1.7471 |

**Table (2). Weight of glacial acetic acid and glutaraldehyde cross linked polymer (5x5 cm patch)**

**Folding endurance:**
Folding endurance of the gel film of 5cm X 5cm patch given in number of times of being able to fold is as follows:

| | 1st | 2nd | 3rd | Mean |
|---|---|---|---|---|
| Glacial Acetic Acid | 161 | 165 | 163 | 163±2.0 |
| Glutaraldehyde | 185 | 189 | 182 | 185±3.51 |

**Table (3). Folding endurance**

## DISCUSSION

Aprepitant is a neurokinin 1 receptor antagonist that is effective against chemotherapy induced nausea and vomiting. It is available in oral and parenteral forms. Studies have shown its efficacy in transdermal delivery in combination with other antiemetics [14].

The Transdermal Drug Delivery System is one of the novel routes for systemic delivery of drugs through the intact skin. The ultimate goal of this dosage design is to maximize the flux through skin and at the same time minimize retention and metabolism of drug in the skin. It also ensures that compounds are delivered, preferably at a specific rate, to the systemic circulation. The Transdermal Drug Delivery System can deliver certain medications to systemic circulation in a more convenient and effective way than conventional dosage form.

Due to its lesser aqueous solubility, the transdermal flux is comparatively lesser when administered individually. Formulating aprepitant in a gel form will increase the transdermal flux. The main barrier in Transdermal Drug Delivery System is the startum corneum (SC) which is the outer most part among the five layers of epidermis. The composition of SC and the morphology is quite unique in nature due to the tight junctions of keratocytes and with no blood vessels so that permeability of drugs through this layer of the skin is less. Due to this permeability problem various types of formulations have been rejected in the field of Transdermal Drug Delivery System. However lecithin organogels shows very promising results in transdermal drug delivery. The Lecithin organogels are viscoelastic, biocompatible, thermodynamically stable in nature. They can be effective for the delivery of hydrophilic, hydrophobic and amphoteric drugs transdermally. Lecithin organogels are composed of three components lecithin (organogellator), a polar solvent and an organic solvent. In LOs reverse cylindrical micelles forms which are the entangled form of three- dimensional (3D) network. After

solubilizing the lecithin in organic liquids such as isopropyl myristate (IPM), isopropyl palmitate (IPP) and others which are nonpolar the lecithin spherical reverse micelles are formed [15]. Due to the broaden tubular micelles formation it leads to hydration of these spherical reverse micelles. These all then entrap in the solution to form a 3D network. Finally to produce a gel from the nonviscous solution the external organic phase needs to be immobilized, keeping thetransparent and optical isotropic nature same like the original one. Pluronic Lecithin Organogels (PLOs) is a type of Lecithin organogels. The main component in PLOs is pluronic F-127 or poloxomer 407, it is a type of triblock copolymer which contains 70% of the polyoxyethylene and the molecular weight is 12500 Da. Permeation enhancers like polyethylene glycol is added which functions as chemical enhancer of transdermal permeation of drug.

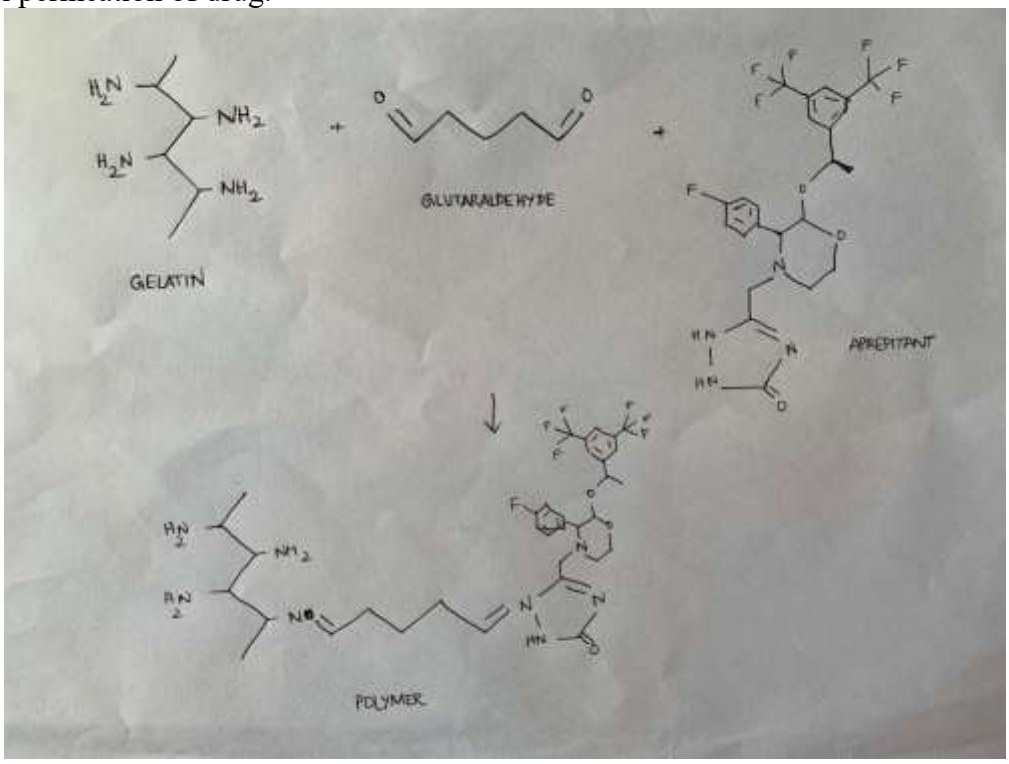


**Figure (13). Structure of cross linked polymer**

Cross linking agents like glutaraldehyde and glacial acetic acid are incorporated to enhance the slow and steady release of drug. Glutaraldehyde has been widely used as cross linker for gelatin. It reacts with gelatin polymer and forms covalent bonds with the amide groups. Cross linker. Then added to a gelatin solution, the reaction between the gelatin amines and the carbonyl groups of glutaraldehyde leads to the formation of a gelatin hydrogel network incorporated with the glutaraldehyde cross-linker molecule. Similarly glacial acetic acid is also used as a cross linker. But the drug release studies show that glutaraldehyde serves the purpose more efficiently when compared to glacial acetic acid.

## CONCLUSION

New transdermal delivery system containing aprepitant had been prepared with satisfactory physicochemical characterization. The drug release pattern could be controlled by changing the cross linker. In this study, we tried to cross link the polymer film using glacial acetic acid as well as glutaraldehyde. Glutaraldehyde cross linking helped in drug release at a slow and steady pace compared to the polymer that was cross linked with. This study confirmed the potential of the designed transdermal delivery system for antiemetic therapy.

## SUMMARY

Transdermal gel technology for antiemetic drug administration is a promising aspect that can be used efficiently in preventing chemotherapy induced nausea and vomiting. A gel formulation of NK1 antagonist antiemetic drug aprepitant was prepared. The efficacy of transdermal delivery of gel

formulation of aprepitant has been increased by the use of penetration enhancers like lecithin and cross linkers like glutaraldehyde andglacial acetic acid that provide better scope for slow and constant delivery of the drug.

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