Research Article

# Transdermal Drug Delivery System of Sodium Cromoglycate

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**ABSTRACT**

The purpose of the present study was to develop matrix type transdermal drug delivery system of sodium cromoglycate using two different polymers, hydroxypropyl methylcellulose (HPMC) and Eudragit L 100 by solvent evaporation technique[1]. Silicon cups were used as a substrate. Polyethylene glycol (PEG) 400 was used as plasticizer. The physicochemical interactions between Sodium cromoglycate and polymers were investigated by Fourier transform infrared (FTIR) spectroscopy. The mechanical parameters like thickness, weight variation, folding endurance, drug content uniformity, percentage moisture absorption and percentage moisture loss were evaluated. *In vitro* drug release studies were carried out using modified Franz diffusion cell. The concentration of diffused drug was measured using UV-visible spectrophotometer at wavelength 326 nm. The effect of polymer concentration on sodium cromoglycate release from the patch was studied. The effect of fabrication method of films on drug release was also investigated. FTIR studies did not show any evidence of interaction between the drug and the polymers. The formulation of hydroxypropyl methylcellulose showed maximum release of 49.3 %, and from Eudragit L 100 formulations 21.3%. There was a significant effect of fabrication method on drug release.

**Keywords:** Sodium cromoglycate, Transdermal Drug Delivery, Solvent evaporation technique, Hydroxypropyl methylcellulose, Eudragit L 100.

## INTRODUCTION

Transdermal drug delivery systems are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin into the bloodstream. An advantage of a transdermal drug delivery route over other types of medication delivery such as oral, topical, intravenous, etc. is that the patch provides a controlled release of the drug into the patient. The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it also known as a monolithic device.

In this study, we try to fabricate sodium cromoglycate matrix type transdermal drug delivery system for prevention of asthma. Asthma is a disease characterized by episodes of obstructive acute bronchial stenosis caused exclusively in breath, cough, chest tightness, wheezing and accelerates respiratory movements. Asthma prevalence rate varies from country to country, with an estimated incidence in most countries around 5% in adults and 10% in children and is more common in urban population. The prevalence of asthma and mortality resulting increased significantly in recent, Despite the progress in diagnostic and therapeutic features. The reason for this is unclear, but it is believed that the civilian life and exposure to dusts and passive smoking may play a role in that. There are about 100-150 million people worldwide suffer from asthma, deaths are estimated annually 180,000 cases, which confirms that there is an urgent need in the world market to try to deliver asthma medication through the dermis in a successful way, which achieves significant economic feasibility. Asthma is a serious disease, since it may start at the early childhood, therefore the patient needs long-term treatment. The use of asthma medications either orally or by inhalation may be associated with a decrease in the plasma concentration of drug below the effective concentration especially between the bedtime dose and the early morning dose; therefore, the patient may wake up at midnight with an asthma attack[2]. The use of transdermal drug delivery system may allow us to avoid these night attacks by maintaining the effective therapeutic concentration of drug in the plasma within the therapeutic window, which is the aim, and significance of our study. Dr. Roger Altounyan[3] who suffered from asthma for a long period of his life has discovered sodium cromoglycate. This invention was of great value, since it decreased the use of steroids in many patients[4]. Sodium cromoglycate is used in the management of chronic asthma; it prevents the release of inflammatory mediators from mast cells through stabilization of mast cell membranes. Oral inhalation of sodium cromoglycate may be associated with many disadvantages such as: cough, throat dryness or irritation, severe wheezing or chest tightness immediately after inhalation, difficulties in the use of inhaler especially in children or elderly people, the fact that the amount of administered drug that reaches the lungs depends on the size of bronchconstriction and presence of mucous plugs in the airways. Sodium cromoglycate is relatively a non-toxic drug for children and pregnant it is (FDA category B).

Sodium cromoglycate is a disodium salt of 1, 3-bis (2-carboxychromon-5-yloxy)-2-hydroxypropane Fig. 1. It is a white-creamy powder with a molecular weight of 512 gm/mol and melting point of 241-242°C. It is very poorly absorbed from the gastrointestinal tract less than 1% of the administered dose after oral administration[5], with short half-life 20-60 min after IV administration, 80 min after oral or nasal inhalation. This requires frequent dosing that decreases patient's compliance. The introduction of sodium cromoglycate has led toward thinking in terms of prophylaxis rather than crisis therapy of asthma. It serves as a prototype molecule for prophylactic treatment. Sodium cromoglycate is also used to treat eye and nasal allergies such as hay fever and is available as eye drops and nasal sprays for this purpose as well as inhalers for asthma prevention; it is also available as capsules for treating food allergies. Based on a study done by M Okumura, K Sugibayashi, K Ogawa, Y Morimoto of skin permeability of water soluble drugs[6]. The permeabilities of several water-soluble drugs such as sodium cromoglycate and others through excised hairless rat skin from their aqueous suspensions were investigated by using newly designed two-chamber diffusion cells. The results of the study suggest that some water-soluble drugs with low molecular weight and high solubility in water might be good candidates for transdermal drug delivery.

Transdermal drug delivery system has many advantages such as (avoid hepatic first pass effect, avoid gastrointestinal absorption problems, non-invasive device, and increase patient compliance). In this research, we try to develop a transdermal drug delivery system of matrix type rather than reservoir since it is easy to fabricate and to avoid the problem of dose dumping. Polymers are the skeleton of transdermal patches[7]. The use of water-soluble film forming polymer (HPMC) allows us to avoid the problems associated with volatile organic solvents that may be flammable or toxic. Eudragit L 100 is an anionic acrylic derivative, it has high crystallization tendency, this increase the need to use plasticizers to increase elasticity and flexibility of the film and prevent cracking. The plasticizer will decrease the connection points between molecules inside polymer network and acts as lubricant between the polymer chains. In this research, PEG 400 was used as plasticizer.

## MATERIALS AND METHODS

### Materials

Sodium cromoglycate was received as a gift samples from Fermion OY, Finland. Hydroxypropyl methylcellulose (HPMC) AN6 was procured from Shin Etsuchemical Co. LTD, Japan. Eudragit L 100 from Rohm Gmbh, Germany. All other chemicals used were of analytical grade.

### Investigation of physicochemical compatibility of sodium cromoglycate and the polymer[8]

The physicochemical compatibility between sodium cromoglycate and polymers used in the films was studied by using Fourier transform-infrared (Bruker® FT-IR Tensor 27) spectroscopy. The FT-IR spectra were recorded in the wavelength region between 4000 and 400 $cm^{-1}$. Then spectra obtained for sodium cromoglycate and physical mixtures of sodium cromoglycate with HPMC were compared with each other.

### Preparation of transdermal patch[9-10]

Matrix type transdermal patches containing sodium cromoglycate were prepared.

### For HPMC formulation

The required amount of HPMC polymer (2%w/w) was dispersed in casting solvent (80 ml water, 20 ml ethanol). Ethanol was used as the co-solvent with water. In addition, ethanol can be used as a permeation enhancer. The beaker was covered to prevent the evaporation of solvent during preparation process. Then the beaker was kept on magnetic stirrer at 500 rpm with the magnetic bead to dissolve the content.

To this mixture, polyethylene glycol (PEG) 400 was added gradually as a plasticizer. It was found to be 30% of dry weight of HPMC polymer[11]. Then sodium cromoglycate was added (0.2 g/100 ml). The dispersion was exposed to ultra sound waves for 7 minutes, to remove entrapped air bubbles[12]. The mixture was left on standing for 1 hour. Then 10 ml of polymeric dispersion of drug was poured into round silicon cups (24.6 $cm^2$). To control the rate of evaporation of casting solvent and prevent cracking of films after drying, silicon cups were covered with glass funnels[12]. The casting solvent was then allowed to evaporate inside an incubator at temperature between 45-50°C for six hours over uniform horizontal surface to obtain film of uniform thickness (0.2 mm). The dried films were easily removed from silicon cups, wrapped in Aluminum-paper and stored in desiccator. Concerning drug concentration in polymeric solution another trial was performed. All the experiment parameters were fixed except drug concentration. The drug concentration in the formula was doubled (0.4g sodium cromoglycate /100 ml of casting solvent), after drying, the films were milky, opaque, and have a wave like structure, to find reason for this there is a need to study morphology and surface topography of films which has strong relation with the evaporation patterns of casting solvents from polymeric solution. This study requires electronic microscope. Since it was not available, we quit this step and maintain the experimental drug concentration that gave us good film appearance (0.2 g sodium cromoglycate/100 ml of casting solvent).

### For Eudragit L 100 Formulation

The fabrication of patches based on Eudragit L100 polymer encountered some technical problems concerning choosing the suitable casting solvent, Table 1.

During drying process, the solvent evaporation will gradually increases the polymer concentration, then the molecules become close to each other and rearrange in a

uniform way. Due to the surface tension polymer, molecules will interact with each other to form a three-dimension network, which gives the polymer its unique mechanical characteristics.

**Evaluation of transdermal patch**[13-14]

***Physical appearance***

After visual examination for all patches, the fabricated films were clear, transparent, smooth, and flexible.

***Thickness uniformity***[15]

The thickness of the formulated films was measured at five different points using (Lezaco®, Dial Thickness gauges), and average thickness and standard deviation were calculated.

***Weight uniformity***

For weight variation test, three films from each batch were selected randomly and weighed individually using a digital electronic balance (Denver instrument AA-200), and the average weight and standard deviation were calculated.

***Folding endurance***[16]

The purpose of this test is to measure the ability of the fabricated film to maintain its integrity when it exposed to natural skin folds.

This test was performed manually for the prepared films. A strip of film (4x2 $cm^2$) was cut and repeatedly folded at the same place between fingers until it broke.

The number of times the film could be folded at the same place without cracking or breaking gave the value of film folding endurance.

***Water absorption capacity***

Also Known as moisture uptake. The films were weighed using digital electronic balance and placed in the desiccator.

Relative humidity was between 80-90% maintains by solution of potassium chloride. After three days, the films were taken out and weighed again. The study was performed at 25°C. The difference between initial weight and final weight of the film was calculated, and then the following equation was applied:

$$\%\ moisture\ uptake = \frac{Film\ final\ weight - Initial\ weight}{Initial\ weight\ of\ film} \times 100\%$$

***Percentage moisture loss***

The chosen films films were weighed using digital balance and kept in a desiccators containing anhydrous calcium chloride. After three days of incubation, the films were taken out and weighed. The difference between initial weight and final weight of the film was calculated, and then the following equation was applied:

$$\%\ moisture\ loss = \frac{Film\ Initial\ weight - Final\ weight}{Initial\ weight\ of\ film} \times 100\%$$

***Drug content uniformity test***

The fabricated patches (1x1 $cm^2$) were cut into small pieces. Then these small pieces were added to a 100 ml beaker of phosphate buffer solution of pH=7.4. The medium was stirred with magnetic bead. The contents were filtered and were assayed for the drug content compared with a reference solution consisting of drug-free films at wavelength 326 nm spectrophotometrically. Sodium cromoglycate concentration was calculated from sodium cromoglycate calibration curve, which study the relation between drug concentration and absorption to ensure linearity, sensitivity of the method as well as correlation coefficient.

***In vitro drug release studies***[17]

First of all the stability of sodium cromoglycate in phosphate buffer pH 7.4 (the receptor medium in Franz diffusion cell) was studied. A modified Franz diffusion cell with a receptor compartment capacity of 19 ml was fabricated to study the *in vitro* sodium cromoglycate release profile from transdermal matrix patches. Water bath temperature was adjusted at 37±2°C to simulate body temperature. For this study, the patches (3.14 $cm^2$) were stuck to an adhesive backing layer, which was slightly larger than the patch to ensure that the receptor fluid could not come in contact with the sides of the film, and to assure unidirectional release of sodium cromoglycate. The face of the film was placed in contact with the receptor fluid pH 7.4 buffer for maintaining sink condition. 3 ml of the receptor fluid was withdrawn at equal intervals. It was immediately replaced with 3 ml of drug-free buffer solution to maintain constant volume. The removed fluid was analyzed spectrophotometrically at wavelength 326 nm and concentration was observed from sodium cromoglycate calibration curve. Fig. 2.

***The effect of polymer concentration on drug release***

The aim of this study was to evaluate the effect of HPMC concentration on drug release. For this study, three groups of films were fabricated with different HPMC concentrations as the following:

**Group A**: HPMC 2g/100 ml of casting solvent.

**Group B:** HPMC 4g/100 ml of casting solvent.

**Group C:** HPMC 6g/100 ml of casting solvent.

*In vitro* drug release studies were performed for each group using Franz diffusion cell. All other experiment parameters were fixed to achieve realistic comparison.

***The effect of fabrication method of films on drug release***

The aim of this study was to evaluate the effect of film fabrication method on drug release. The study discussed two fabrication methods, X method, and Y method, both methods depend on solvent casting technique, all other

experimental parameters were fixed. X method, was the same fabrication method mentioned at the beginning of this research, the HPMC polymer was directly added to the total volume of casting solvent at room temperature. While the other method (Y method) evaluates the effect of solvent temperature on polymer behavior and solubility, which may affect drug release. For Y method: after heating quarter of the total water volume (20 ml) to 80-90°C, the HPMC polymer was dispersed in this hot water, after that the rest volume of casting solvent (60 ml water, 20 ml ethanol) was added after cooling at a refrigerator, then the procedure continued as in X method.

## RESULTS AND DISCUSSION

### Results of thickness measurements

Low standard deviation values indicate uniformity of thickness in the films fabricated by solvent casting method. Table 2.

### Results of weight measurements

The films weights ranged between 0.363 ± 0.021 g and 0.415 ± 0.016 g, which indicates that there was no significant weight variation between patches. Table 2.

### Results of folding endurance

Folding endurance was found to be > 150.

### Results of water absorption capacity

Low moisture uptake increases film stability and decreases the possibility of microbial growth. Table 2.

### Results of percentage moisture loss

The small moisture loss in the films prevents complete drying of films. Table 2.

**Results of drug content uniformity of films:** Table 2.

### Results of physicochemical compatibility of sodium cromoglycate and polymer

A physical mixture of sodium cromoglycate and HPMC polymer was prepared.

Fourier transform infrared spectroscopy results FTIR spectra maintain all the bands of sodium cromoglycate, which indicates that there was no change in the functional groups of sodium cromoglycate in this mixture.

This result suggests that there is no interaction between drug and polymer used.

### Results of *In vitro* drug release studies from HPMC matrices

In our device, sodium cromoglycate was incorporated in a matrix.

The composition of this polymeric matrix could direct drug release.

In addition, the diffusion process of sodium cromoglycate through the matrix is affected by the degree of cross-linking between matrix molecules which in terms affects the diffusion path length through the three dimensional network of polymer chains.

The cumulative percent of sodium cromoglycate released was found to be the highest (49.30%).

### Results of *In vitro* drug release studies from Eudragit L 100 matrices

Highly water-soluble drug formulated with HPMC matrices, it may be characterized with an initial burst effect (20.00%).

While there was no burst effect in Eudragit L 100 formulation (0.11%). Therefore, we can suggest that mixing of Eudragit L 100 polymer with HPMC polymer could enhance the release profile.

Since the addition of Eudragit polymer will decrease the penetration of water into the matrix, decreases the diffusion of sodium cromoglycate, and slower initial release. The decrease in the cumulative percentage of drug release from Eudragit polymer (21.30%), compared with (49.30%) in HPMC formulation may be due to the high binding potential of Eudragit polymer for drug. Table3, Fig1.

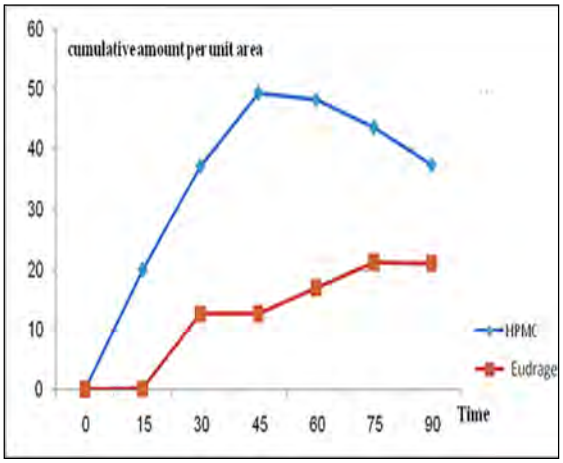


**Figure 1:** Comparison of drug release between HPMC films and Eudragit L 100 films.

### Results of the effect of polymer concentration on drug release

From the results we can notice that, for group B: the increase in polymer concentration, increased the cumulative percentage of drug release (59.77%) compared with group A (49.30%). The reason was that the increase of HPMC concentration increased the amount of water uptake, therefore increased polymer hydration to a certain accepted limits, hence increased drug release. On the other hand, the huge increase of polymer concentration in group C, decreased the cumulative percent of drug release (34.30%) which is even less than group A. Since the polymer is a dynamic three-dimensional network, this big increase in its concentration, increased the interactions between its molecules, which in terms increased the viscosity of the

polymer as well as diffusion path length, which is inversely proportional to the rate of diffusion. Table 4,5. Fig.2.

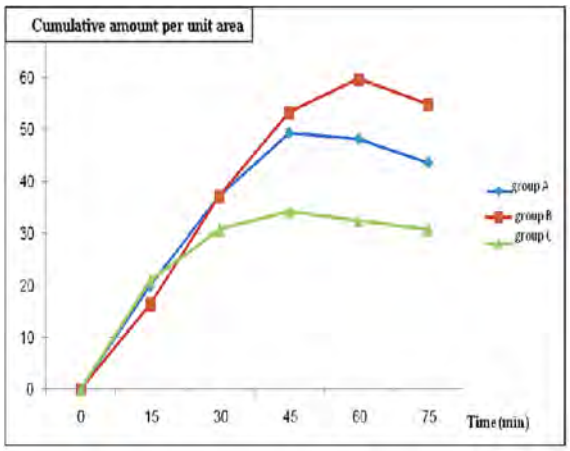


**Figure 2:** Comparison between groups A, B, and C

**Results of the effect of fabrication method on drug release**

There was an increase in the cumulative percentage of sodium cromoglycate released from patches fabricated applying method Y (69.12%) compared with (49.30%) for X method. On the other hand, the increasing pattern of drug release was more consistent in X method rather than Y method. An increase in initial burst effect could also be noticed in Y method (41.08%) compared to X method (20.00%). HPMC polymer is more soluble in cold water than in hot water. Therefore, in Y method, we disperse HPMC in hot water (80-90°C), in order to disperse particles before their outer layer becomes swollen. Then the rest of cold water, which is the ideal solvent of HPMC, was added to cool the suspension and dissolve the dispersed particles faster with less shear force[18]. Fig.3.

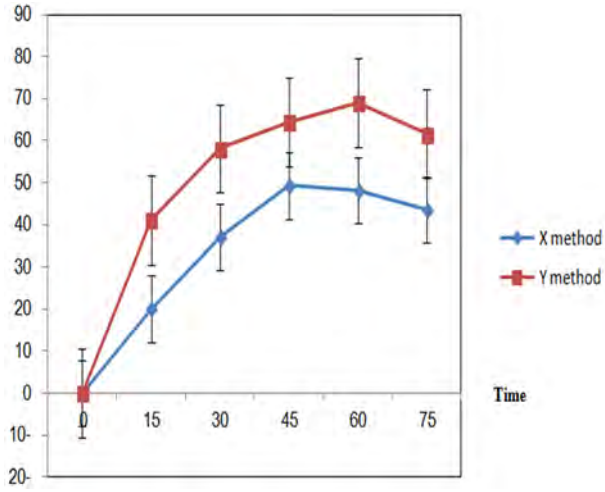


**Figure 3:** Comparison between X and Y methods

## CONCLUSION

In conclusion, controlled release matrix type transdermal drug delivery system of sodium cromoglycate can be considered as a promising system, mixing of Eudragit L100 polymer with HPMC polymer could have potential to formulate TDDS. However, the pharmacodynamic and pharmacokinetic assessment of these systems in animals and human volunteers is necessary to achieve the desired release profile of sodium cromoglycate.

**Table 1:** Eudragit L 100 suggested formulas.

| | Experiment 1 | Experiment 2 | Experiment 3 |
|---|---|---|---|
| **Eudragit L 100** | 2 g | 2 g | 2 g |
| **Sodium cromoglycate** | 0.2 g | 0.2 g | 0.2 g |
| **PEG 400** | 0.6 g | 0.6 g | 0.6 g |
| **Casting solvent** | 96 ml isopropyl alcohol, 4 ml water | 60 ml isopropyl alcohol, 40 ml water | 40 ml dichloromethane, 60 ml isopropyl alcohol |
| **Result** | brittle films/ **rejected** | Brittle, opaque, milky films/ **rejected** | Good flexible, transparent films/ **accepted** |

**Table 2:** Films mechanical parameters.

| Film code | Thickness (mm) | Weight (g) | % moisture absorption | % moisture loss |
|---|---|---|---|---|
| **1** | 0.204 ± 0.021 | 0.395 ± 0.014 | 6.582 ± 2.021 | 13.164 ± 0.021 |
| **2** | 0.213 ± 0.012 | 0.389 ± 0.012 | 7.969 ± 0.014 | 11.311 ± 0.014 |
| **3** | 0.210 ± 0.016 | 0.38 ± 0.0156 | 7.532 ± 1.012 | 12.207 ± 0.012 |
| **4** | 0.196 ± 0.024 | 0.363 ± 0.021 | 6.336 ± 0.014 | 12.947 ± 0.013 |
| **5** | 0.206 ± 0.012 | 0.415 ± 0.016 | 6.746 ± 1.022 | 12.048 ± 2.51 |

**Table 3:** Comparison of % drug release between HPMC films and Eudragit L 100 films.

| Cumulative % release | |
|---|---|
| **HPMC films** | **Eudragit L 100 films** |
| 20.00 | 0.11 |
| 37.10 | 12.63 |
| 49.30 | 12.73 |
| 48.17 | 17.02 |
| 43.60 | 21.30 |
| 37.30 | 21.06 |

**Table 4:** *In vitro* sodium cromoglycate release from HPMC matrices (Group B)

| Sample number | Conc.(mg/ml) | Absorbance | % release |
|---|---|---|---|
| 1 | 0.0217871 | 0.372685 | 16.39 |
| 2 | 0.0494269 | 0.845486 | 37.18 |
| 3 | 0.0709337 | 1.21338 | 53.36 |
| 4 | 0.0794497 | 1.35905 | 59.77 |
| 5 | 0.0728283 | 1.24579 | 54.79 |
| 6 | 0.0636928 | 1.08952 | 47.92 |
| 7 | 0.0563886 | 0.964571 | 42.42 |
| 8 | 0.0466902 | 0.8069862 | 35.12 |

**Table 5:** *In vitro* sodium cromoglycate release from HPMC matrices (Group C)

| Sample number | Conc.(mg/ml) | Absorbance | % release |
|---|---|---|---|
| 1 | 0.0266291 | 0.455512 | 21.00 |
| 2 | 0.0388622 | 0.664768 | 30.80 |
| 3 | 0.0431987 | 0.738948 | 34.32 |
| 4 | 0.0409345 | 0.70012 | 32.52 |
| 5 | 0.0387473 | 0.65768 | 30.78 |

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