PREPARATION AND EVALUATION OF TRANSDERMAL PATCH OF DESLORATADINE

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ABSTRACT
Transdermal patches are innovative drug delivery systems and can be used for achieving efficient systemic effect by passing hepatic first pass metabolism and increasing the fraction absorbed. The transdermal therapeutic system provide for continuous drug release through intact skin into the systemic blood stream during a prolong time at a preset rate. Desloratadine, on oral administration, may cause many adverse effects such as headache, fatigue, dryness of mouth, nose or throat, nausea, vomiting, drowsiness etc. and it is also poorly water soluble, so it shows dissolution rate limited absorption. To avoid these problems, the matrix type transdermal patches of Desloratadine are prepared by solvent casting technique on mercury substrate. For this purpose transdermal patches were prepared by using film forming polymer such as HPMC 6 cps with PG as a plasticzer by solvent evaporation technique. The patches produced were found to be satisfactory in terms of physicochemical properties like appearance, thickness, weight variation, folding endurance, moisture content, tensile strength, percent elongation at break and percent drug content. Prepared patches exhibited zero order kinetics permeation of the drug from the patches was governed by a diffusion mechanism. Drug-excipient interaction studies will be carried out using FTIR technique. The optimized batch (F7- HPMC 6 cps 6% and PG 3%) was subjected to stability studies for a period of 1 month. The results indicated that there was no appreciable change in the values of in vitro diffusion profile.

KEY WORDS: Desloratadine, matrix type of transdermal patch, HPMC 6 cps

1. INTRODUCTION

Transdermal drug delivery systems are formulations that are applied to the body surface and are designed to deliver the active drug across the skin, into the systemic circulation. Conventional systems of medication which require multi-dose therapy are not without problems. The newer approach to drug delivery is to deliver drug into systemic circulation at a pre determined rate, known as controlled release drug delivery system. The impetus for the development of newer/novel drug delivery systems, apart from therapeutic efficacy is cost. The developmental cost of a new drug may be about $ 250 million (Rs. 900 crores) and takes about 12 years to reach the market place. Where as an existing drug molecule can get a second life with newer drug delivery systems that can be
developed in half of the time with 20% cost of the new drug discovery. Novel techniques for drug delivery have been investigated in human medicine in recent years. Among the new drug delivery systems is the use of transdermal applications. In addition to being user friendly, these therapeutics are safe, efficacious and may improve patient treatment compliance. Pharmacologic considerations including avoiding first pass effect and biotransformation may also be important advantages of transdermal administration. These advantages may easily be applied to the veterinary patient. Although limited studies have been conducted using this route of administration in veterinary patients many agents are currently being used empirically. The development of TDDS is multidisciplinary activity that encompasses fundamental feasibility studies starting from the selection of drug molecule to the demonstration of sufficient drug flux in an ex vivo and in vivo model followed by fabrication of a drug delivery system that meets all the stringent needs that are specific to the drug molecule (physicochemical and stability factors), the patient (comfort and cosmetic appeal), the manufacturer (scale up and manufacturability) and most important the economy.

The choice of drugs to be delivered transdermally is the most difficult one and careful consideration should be given to their selection. The important criteria that should be considered in this process are the drug properties such as its skin permeability, molecular weight, melting point, partition coefficient and its potency. Based on the clinical need and the above said criteria, antihistamine drug Desloratadine has been selected for the development of TDDS in the present work. The treatment of cold and flu is one of the leading problems in medicine today. Desloratadine blocks the action of endogenous histamine, which subsequently leads to temporary relief of the negative symptoms (eg. nasal congestion, watery eyes) brought on by histamine.

2. MATERIAL AND METHODS

Desloratadine was obtained as a gift sample from Micro Labs Ltd, Banglore. HPMC 6 cps, Propylene glycol and other chemicals used were of analytical grade.

2.1. PREPARATION OF THE PATCHES

Transdermal patches containing Desloratadine were prepared by the solvent casting method. HPMC 6 cps in selected ratios were weighed and dissolved in solvent system of ethanol and DCM(2:1). The plasticizer was added to the polymeric solution and mixed uniformly for 30 min using magnetic stirrer. Finally the drug was incorporated with continuous agitation. The patches were prepared by casting the drug loaded polymeric solutions in a petridish. The casting solution was dried at room temperature for a period of 12 hrs. Then the patches were cut into 1x1 cm² patches. The dried patches were packed in aluminum foil and stored in desiccators till further studies. A 3² full factorial design was used in this study and two factors were evaluated, each at three levels; experimental batches were performed at all nine possible combinations as shown in Table 1. Coded values for 3² Full factorial design are shown in Table 2. A 2-factor 3-level factorial experimental design technique was employed to investigate the dependent variables like percent
cumulative drug release using the Design Expert Software (Version 7.1.4).

2.2. EQUATIONS RELATING INDEPENDENT VARIABLES AND RESPONSES

The equations relating independent variables and responses were obtained by subjecting the results to statistical evaluation. Microsoft Excel version 2007 was used to perform multiple linear regression to determine the control factors that significantly affect the responses.

Independent Variables: HPMC 6 cps

Responses: % drug release.

Polynomial equation for 3² full factorial designs
Y = b₁X₁ + b₂X₂ + b₁₁X₁² + b₂₂X₂² + b₁₂X₁X₂

The significant factors in the equations were selected using a stepwise forward and backward elimination for the calculation of regression analysis. The terms of full model having non-significant p value (p > 0.05) have negligible contribution in obtaining dependent variables and thus are neglected.

3. EVALUATIONS

Physical appearance.
All the transdermal patches were visually inspected for color, clarity, flexibility and smoothness.

Thickness
The thickness of patches was measured at three places using a micrometer (Mitutoyo Co., Japan) and mean values were calculated.⁹

Weight uniformity
For each formulation, three randomly selected patches were used. For weight variation test, 3 films from each batch were weighed individually and the average weight was calculated.⁹,¹⁰

Folding Endurance
This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance.¹²

Tensile strength
A small film strip (40 x 15 mm) was used. One end of the strip was fixed between adhesive tapes to give support to the film when placed in the film holder. Another end of the film was fixed between the adhesive tapes with a small pin sandwiched between them to keep the strip straight while stretching. A small hole was made in the adhesive tape near the pin in which a hook was inserted. A thread was tied to this hook, passed over the pulley and a small pin attached to the other end to hold the weights. A small pointer was attached to the thread, which travels over the graph paper affixed on the base plate. To determine the tensile strength, the film was pulled by means of a pulley system. Weights were gradually added to the pan to increase the pulling force till the film was broken. The weight required to break the film was noted as break force.¹³⁻¹⁴

Percent elongation at break (%E)
Percent elongation at break (%E) is calculated by dividing the extension at the moment of rupture of the specimen by the initial gage length of the specimen and multiplying by 100.¹⁵

Moisture content
The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 hrs. The films are
weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula:\[16\]

\[
\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100
\]

**Drug content analysis**
The patches (1cm\(^2\)) were cut and added to a beaker containing 100 mL of phosphate buffered saline of pH 7.4. The medium was stirred with magnetic bead. The contents were filtered using whatmann filter paper and the filtrate was examined for the drug content against the reference solution consisting of placebo films (contains no drug) at 243.5 nm spectrophotometrically. The experiment was repeated to validate the result.\[17\]

**In Vitro Diffusion study**
The in vitro diffusion study was conducted using a Franz diffusion cell receptor compartment capacity: (22 ml). The receiver compartment was filled with 22 ml of phosphate buffer, pH 7.4. The transdermal patch was firmly pressed onto the centre of the cellophane membrane and then the membrane was mounted on the donor compartment. The donor compartment was then placed in position such that the surface of membrane just touches the receptor fluid surface. The whole assembly was kept on a water bath maintained at 32 ± 1 ºC. The samples were withdrawn at different time intervals up to 12 hrs and analyzed for drug content. Receptor phase was replenished with an equal volume of buffer solution at each time interval.\[18\]

**Stability study**
Stability study was carried out for optimized patch formulation at 40ºC temperature, 75% RH in a humidity chamber for 1 month. After 1 month samples were withdrawn and evaluated for in vitro drug release study.

4. **RESULTS**
All the results are shown in the tables 4 to 9.

5. **DISCUSSION**
The patches produced were found to be satisfactory in terms of physicochemical properties like appearance, thickness, weight variation, folding endurance, moisture content, tensile strength, percent elongation at break and percent drug content. The patch of F7 batch shows the maximum drug release in 24 hrs. then the other batches. The F7 batch also show the best physical appearance and folding appearance. All batches show good tensile strength in range of 0.28-.32 kg/mm\(^2\).

FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. Infrared (IR) spectra of Deslorataadine, physical mixture of Deslorataadine and HPMC 6 cps are shown in Figure 4 and 5 respectively. From the figure, it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers.

The cumulative amount of drug permeated per square centimeter of patches through membrane was plotted against time was fitted to zero, first, higuchi and peppas kinetic model. As indicated in Table 8, the release profile of Deslorataadine followed zero-order kinetics in all formulations. However, the release profile of the optimized
formulation 7 ($r^2 = 0.982$ for zero order) indicated that the permeation of the drug from the patches was governed by a diffusion mechanism. Similarity factor of the patch was 74.0274 which indicate that path is stable.

6. CONCLUSION

From the results obtained so far it can be concluded that HPMC 6 cps in concentration of 6% with propylene glycol 3% w/w as plasticizer are promising controlled release transdermal drug delivery system for Desloratadine. Prepared patches exhibited zero order kinetics permeation of the drug from the patches was governed by a diffusion mechanism.

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| Formulation Code | Variables |
|------------------|-----------|
|                  | X1        | X2        |
| H1               | -1        | -1        |
| H2               | -1        | 0         |
| H3               | -1        | 1         |
| H4               | 0         | -1        |
| H5               | 0         | 0         |
| H6               | 0         | 1         |
| H7               | 1         | -1        |
| H8               | 1         | 0         |
| H9               | 1         | 1         |
### Table 2: Coded values for $3^2$ Full factorial design

| Coded values | X1  | X2  |
|--------------|-----|-----|
| -1           | 300 | 120 |
| 0            | 500 | 150 |
| 1            | 700 | 180 |

### Table 3: $3^2$ Factorial design of transdermal patch of Desloratadine

| Batch | Drug (mg) | HPMC 6 cps (mg) | Plasticizer/Penetration enhancer (PG) ml |
|-------|-----------|-----------------|------------------------------------------|
| F1    | 105.9     | 6               | 1                                        |
| F2    | 105.9     | 8               | 1                                        |
| F3    | 105.9     | 10              | 1                                        |
| F4    | 105.9     | 6               | 2                                        |
| F5    | 105.9     | 8               | 2                                        |
| F6    | 105.9     | 10              | 2                                        |
| F7    | 105.9     | 6               | 3                                        |
| F8    | 105.9     | 8               | 3                                        |
| F9    | 105.9     | 10              | 3                                        |
### Table 4: Physicochemical data of Desloratadine transdermal patch

| Batch code | Physical Appearance | Thickness (mm) | Weight variation (mg) | Folding endurance |
|------------|---------------------|---------------|-----------------------|------------------|
| F1         | ++                  | 36.65±1.2     | 65.26±1.3             | 160±1.7          |
| F2         | +++                 | 33.40±1.4     | 62.50±1.5             | 180±2            |
| F3         | ++                  | 32.54±1.6     | 67.02±1.8             | 200±1.2          |
| F4         | +++                 | 37.77±1.4     | 66.25±1.4             | 180±1.8          |
| F5         | ++                  | 38.24±1.6     | 66.89±1.6             | 227±1.3          |
| F6         | +++                 | 29.54±1.7     | 63.05±1.6             | 185±1.6          |
| F7         | +++                 | 29.78±1.5     | 66.67±1.9             | 241±1.9          |
| F8         | ++                  | 32.87±1.4     | 65.87±1.4             | 150±1.1          |
| F9         | +++                 | 28.72±1.9     | 64.61±1.7             | 180±1.6          |

### Table 5: Physicochemical data of Desloratadine transdermal patch

| Batch code | %Drug content | % Moisture content | Tensile strength | % elongation at break |
|------------|--------------|--------------------|-----------------|----------------------|
| F1         | 98.24±1.2    | 4.4±1.2            | 0.285±0.25      | 18.22±0.23           |
| F2         | 97.21±1.5    | 4.7±0.9            | 0.294±0.14      | 15.33±0.89           |
| F3         | 96.45±1.9    | 5.02±1.8           | 0.311±0.05      | 22.66±0.36           |
| F4         | 94.39±1.1    | 5.15±1.5           | 0.290±0.40      | 21.43±0.67           |
| F5         | 96.69±1.4    | 3.3±1.3            | 0.299±0.25      | 24.95±0.39           |
| F6         | 95.47±2.1    | 4.2±1.9            | 0.317±0.15      | 26.73±0.84           |
| F7         | 98.89±1.3    | 3.9±0.5            | 0.305±0.20      | 24.45±0.55           |
| F8         | 97.47±1.7    | 4.1±0.6            | 0.311±0.18      | 26.91±0.70           |
| F9         | 97.71±0.8    | 4.4±1.1            | 0.317±0.84      | 27.45±0.64           |
Table 6: Release profile of factorial batches (F1-F5)

| Time | % cumulative drug release |
|------|---------------------------|
|      | F1  | F2  | F3  | F4  | F5  |
| 0    | 0   | 0   | 0   | 0   | 0   |
| 0.25 | 5.31±0.56 | 4.70±0.26 | 3.91±0.87 | 5.83±0.65 | 4.96±0.55 |
| 0.50 | 5.78±0.42 | 5.66±0.59 | 5.35±0.35 | 7.37±0.54 | 6.45±0.89 |
| 1    | 8.17±0.94 | 7.44±0.78 | 6.86±0.95 | 9.25±0.85 | 9.50±0.75 |
| 2    | 9.98±0.82 | 9.47±1.06 | 8.78±0.63 | 12.07±1.5 | 14.09±0.5 |
| 4    | 11.90±1.5 | 11.34±1.4 | 11.48±0.5 | 18.16±1.5 | 20.38±0.85 |
| 6    | 20±0.98 | 19.12±1.2 | 17.62±1.4 | 28.05±1.8 | 29.60±1.6 |
| 8    | 33.56±1.3 | 30.53±1.4 | 28.43±1.5 | 39.3±1.75 | 41.01±1.9 |
| 10   | 42.07±1.4 | 40.95±1.5 | 39.09±1.8 | 49.44±1.9 | 53.50±1.2 |
| 12   | 44.78±1.3 | 51.07±1.3 | 50.78±1.6 | 59.08±1.5 | 63.61±1.5 |
| 18   | 63.45±1.8 | 64.79±0.7 | 65.63±1.5 | 72.43±1.5 | 73.09±1.8 |
| 24   | 87.41±1.5 | 84.23±1.4 | 79.37±1.8 | 91.50±1.5 | 88.32±1.9 |
Table 7: Release profile of factorial batches (F6-F9)

| Time | % cumulative drug release |
|------|---------------------------|
|      | F6 | F7 | F8 | F9 |
| 0    | 0  | 0  | 0  | 0  |
| 0.25 | 4.79±0.26 | 6.18±0.39 | 6.00±0.82 | 5.05±0.73 |
| 0.50 | 6.27±0.89 | 8.79±0.27 | 7.73±0.73 | 6.46±0.83 |
| 1    | 8.78±0.59 | 10.13±0.83 | 9.54±0.91 | 9.15±0.87 |
| 2    | 11.76±1.16 | 12.4±0.74 | 12.03±1.17 | 11.11±1.28 |
| 4    | 18.98±1.57 | 18.94±1.34 | 18.46±1.49 | 18.02±1.67 |
| 6    | 26.39±1.24 | 29.82±1.19 | 27.84±1.72 | 25.81±1.37 |
| 8    | 37.11±1.06 | 41.41±1.58 | 38.90±1.43 | 36.86±1.83 |
| 10   | 47.06±1.85 | 51.48±1.96 | 49.45±1.86 | 45.84±1.71 |
| 12   | 59.54±1.49 | 62.26±1.82 | 60.48±1.75 | 58.43±1.51 |
| 18   | 71.72±1.71 | 75.32±1.91 | 73.82±1.92 | 71.25±1.80 |
| 24   | 85.35±1.84 | 97.52±1.83 | 93.65±1.89 | 87.56±1.89 |
Table 8: Drug release kinetics for the various formulations of transdermal patch

| Formulation | Zero order | First order | Higuchi Model | Peppas Model |
|-------------|------------|-------------|---------------|--------------|
| F1          | 0.989      | 0.739       | 0.85          | 0.943        |
| F2          | 0.985      | 0.751       | 0.858         | 0.955        |
| F3          | 0.981      | 0.761       | 0.858         | 0.965        |
| F4          | 0.981      | 0.685       | 0.904         | 0.927        |
| F5          | 0.961      | 0.665       | 0.927         | 0.931        |
| F6          | 0.974      | 0.690       | 0.912         | 0.940        |
| F7          | 0.982      | 0.675       | 0.902         | 0.918        |
| F8          | 0.983      | 0.686       | 0.899         | 0.926        |
| F9          | 0.981      | 0.697       | 0.902         | 0.939        |

Table 9: Results of stability study

| Time | %Drug release at 0 Month | %Drug release after 1 Month |
|------|--------------------------|----------------------------|
| 0    | 0                        | 0                          |
| 0.25 | 6.18                     | 7.58                       |
| 0.50 | 8.79                     | 9.65                       |
| 1    | 10.13                    | 11.21                      |
| 2    | 12.74                    | 14.48                      |
| 4    | 18.94                    | 22.17                      |
| 6    | 29.82                    | 33.38                      |
| 8    | 41.42                    | 45.67                      |
| 10   | 51.49                    | 55.42                      |
| 12   | 62.26                    | 68.20                      |
| 18   | 75.32                    | 79.28                      |
| 24   | 97.52                    | 99.69                      |
Figure 1: Thickness and weight variation of different batches

Figure 2: Folding endurance and % drug content of different batches
Figure 3: Tensile strength, % elongation at break and % moisture content of different batches.

Figure 4: FTIR spectra of Desloratadine.
Figure 5: FTIR spectra of physical mixture of Desloratadine and HPMC

Figure 6: Release profile of Desloratadine from factorial patches
Figure 7: Contour plot showing effect of X1 and X2 % CDR

Figure 8: Surface plot showing effect of X1 and X2 on % CDR