IN-VITRO DRUG RELEASE BEHAVIOR OF PVP/_GUAR GUM POLYMER BLEND TRANSDERMAL FILM WITH DICLOFENAC POTASSIUM

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ABSTRACT
Drug release behavior of Polyvinylpyrrolidone (PVP)/ Guar gum (GG) polymer blend patches with Potassium Diclofenac as model drug was investigated. Drug entrapped polymer blend film were prepared using different ratios of PVP & GG polymers by solvent evaporation technique. In vitro drug release profile of the film was studied by open glass diffusion cell at 37 ± 1°C and release rate was determined by UV double beam spectrophotometer. The release profile follows non-Fickian model and drug release become sustained as concentration of guar gum increases in the polymer matrix.

Keywords: Transdermal drug delivery, PVP, Guar gum, In-vitro drug release.

INTRODUCTION
Drug delivery through transdermal route is one of the promising approaches to by pass hepatic first pass metabolism of drug and to increase therapeutic effect. In transdermal drug delivery system skin is a port for drug administration to provide continuous drug infusion in to systemic circulation. Among the various type of transdermal drug delivery systems available, transdermal drug delivery using thin polymer membrane are widely studied recently. The drug containing polymer matrix patches are placed in a particular region on the body and drug is steadily infused through skin into the systemic blood stream. The process involved added advantages such as maintenance of constant and prolonged drug level hence reduces frequency of dosing, ability to avoid problems of gastric irritation & reduce the risk of systemic side effects by minimizing plasma concentrations. Drug release rate and bioavailability were influenced by nature of drug reservoir used. Transdermal films fabricated by biopolymer have received much attention due to their excellent biocompatibility and biodegradation. Usually synthetic or natural biopolymers are alone may not possess the required properties of biomaterials. Synthetic polymers possess wide range of mechanical properties, transformation process, and low production cost but low biocompatibility where as biological polymers possess good biocompatibility but mechanical properties are often poor. Therefore blends of polymer or cross linked polymer are used as drug carrier to achieve controlled release of drug and to enhance biocompatibility. In the present investigation drug release profile of Potassium Diclofenac is studied with Guar gum and PVP blend polymer as carrier.

Guar gum is a naturally obtained polysaccharide extracted from the endosperm of cyanopsis tetragonolobus. Structurally it is a galactomannan with a galactose to mannose ratio of approximately 1:2. Guar gum is one of the most promising dietary fibers, easily soluble in cold water and has high viscosity at low concentration. Hence it is widely used as thickener and emulsion stabilizer in food, cosmetic and pharmaceuticals. PVP is a biocompatible water soluble polymer also soluble in wide range of organic solvents. It has good complexing ability, film forming ability and adhesive qualities. It is non toxic, inert for living organism hence widely used in various pharmaceutical applications also used in cosmetic, textile, toiletry & paper industry. Diclofenac is an important non steroidal anti inflammatory drug. It undergoes extensive first pass metabolism and only 50% of an orally administered dose is systemically available. Its apparent half life of elimination from the synomial fluid is 3-6hrs and the terminal plasma life is 1-3 hrs.

MATERIALS & METHODS
Polymers employed for the present study are Guar gum purchased from Merck limited Mumbai, and Polyvinylpyrrolidone from Hi Media laboratories Mumbai, mol.wt: 4000. Diclofenac potassium was obtained as gift sample from Arthi drugs Mumbai.

Preparation of Drug entrapped polymer film
The drug containing polymer films were prepared by solution casting method with GG and PVP as polymer matrix in different blend compositions. GG & PVP were dissolved in water to get 1% aqueous polymeric solution. 0.25mg (w/v) drug was incorporated & the solution was stirred until all drug get dissolved. The prepared polymeric solution was poured on a cleaned teflon coated petri dish & dried in a dust free chamber at 40°C. The dried films of different formulations were peeled off, put in self lock covers and stored in a desiccator until further study.

FTIR analysis
In order to characterize drug polymer interaction, IR spectra of pure drug and its formulation with polymer blend were obtained by FTIR spectrometer (NICOLET AVATAR).

Physicochemical characterization of formulation
1. Thickness and weight variation
The patch thickness was measured by a digital micrometer; averages of 5 readings were recorded. Three randomly selected patches were weighed accurately and average weight was calculated.

2. Content uniformity
A known area of each film was weighed accurately, dissolved in 50ml phosphate buffer (pH 7.2) and filtered. The drug content in each formulation was analyzed using UV-VIS double beam spectrophotometer at A max 276nm wave length. The extract of films without drug was used as blank. Average of three readings was recorded.

3. Moisture content
The polymer film patches were weighed individually and kept in a desiccator containing fused calcium chloride for 24hrs. The patches were then reweighed until a constant weight was obtained. The percentage of moisture content was calculated as the difference between final and initial weight with reference to final weight.

4. Moisture absorption
The weighed film patches were kept in a desiccator containing fused calcium chloride at room temperature for 24hr. The patches were then exposed to 84% relative humidity in a desiccator containing saturated solution of potassium chloride until a constant weight for the film was obtained. The percentage of moisture absorption was calculated as the difference between final and initial weight with respect to initial weight.
In vitro drug release studies

Drug release studies were carried out in an open glass diffusion tube. A specimen of dimension 1 cm$^2$ was fixed to hydrated cellophane membrane at one end of diffusion tube and placed in the receptor compartment containing buffer solution of pH 7.2. The assembly was placed on a magnetic stirrer and stirred at 100 rpm. The temperature of the system was maintained at 37±1°C. A known amount of receptor medium was withdrawn at regular intervals of time and sink condition was maintained by replacing equal volume of fresh buffer. The drug concentration was determined by measuring the absorbance of the solution at 276.0 nm$^9$.

Kinetics of drug release

In order to have an insight into the kinetics and mechanism of drug release behavior of the films Higuchi’s model$^{10}$ (Eq.1) and Koresmeyer- Peppas model$^{11}$ (Eq.2) are fitted into the kinetic data of drug release.

\[
\frac{M_t}{M_\infty} = kt^{1/2}
\]  

(1)

According to Higuchi’s model, an inert matrix provides sustained drug release over a reasonable period of time and yields a reproducible straight line when the fraction of the drug release is plotted versus the square root of time if the drug release were diffusion controlled.$^{10,13}$

\[
\frac{M_t}{M_\infty} = kt^n
\]  

(2)

where $M_t$ and $M_\infty$ correspond to the amount of drug released at time $t$ and after an infinite time respectively. $k$ is a constant related to the structural and geometrical properties of the drug release system and $n$ is diffusional exponent. The value of diffusional exponent provides information about different release mechanisms. When $n<0.5$, the solvent diffuses through and the drug is released through film by Quasi-Fickian diffusion mechanism, $0.5<n<1$ for non-Fickian model or anomalous diffusion and when $n \geq 1$ indicates zero order release.$^{11-14}$

RESULT AND DISCUSSION

The matrix film of drug polymer formulations were prepared by solution casting method and dried films were analyzed for their physicochemical characteristics such as thickness, weight variation, % of moisture content, % of moisture uptake and content uniformity and results were given in Table 1. The thickness of the film was varied from 172µm to 155µm with small standard deviation ensured uniformity of film prepared by solution casting method. The weights of 1cm$^2$ film were found to be more or less similar. The percentage of moisture content found between 14.18 to 15.3, and % of moisture uptake found between 21.90 and 25.47. The result reveals that % of moisture content and moisture uptake increases with increase in PVP content in the film.

Table 1: Characterisation of prepared transdermal film.

<table>
<thead>
<tr>
<th>Weight ratio of GG/PVP (%)</th>
<th>Weight Variation (mg) Mean ± SD$^*$</th>
<th>Average drug content (mg) Mean ± SD$^*$</th>
<th>Thickness(µm) Mean ± SD$^*$</th>
<th>Moisture content (Wt %) Mean ± SD$^*$</th>
<th>Moisture uptake (Wt %) Mean ± SD$^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>70/30</td>
<td>14.9±0.0300</td>
<td>6.38±0.3036</td>
<td>155±0.01030</td>
<td>14.18</td>
<td>21.90</td>
</tr>
<tr>
<td>60/40</td>
<td>13.1±0.1026</td>
<td>5.77±0.6400</td>
<td>172±0.01083</td>
<td>14.55</td>
<td>24.47</td>
</tr>
<tr>
<td>50/50</td>
<td>16.3±0.2510</td>
<td>6.35±0.2000</td>
<td>170±0.02410</td>
<td>14.60</td>
<td>24.87</td>
</tr>
<tr>
<td>40/60</td>
<td>18.3±0.0305</td>
<td>8.70±1.3000</td>
<td>165±0.00798</td>
<td>15.30</td>
<td>25.47</td>
</tr>
</tbody>
</table>

Content uniformity

In order to ascertain uniformity in the distribution of drug in polymer membrane, content uniformity test was performed. Results of the analysis were given in Table1. Content uniformity values vary from 5.77 mg to 8.70 mg with small standard deviation (Expected range as per Indian Pharmacopoeia (IP) standard is 1-9 mg/cm$^2$). It clearly indicated that the drug was uniformly distributed throughout the film.$^1$

FTIR analysis

FTIR spectra of Diclofenac potassium and its formulation with GG/PVP polymer blend are shown in figure 1. The characteristic peak of Diclofenac potassium observed at wave number 3246.5 cm$^{-1}$ (N-H), 3022.8 cm$^{-1}$ (=C-H), 1570.8 cm$^{-1}$ & 1274.4 cm$^{-1}$ (C=O) & 741.0 cm$^{-1}$ (-Cl). The same peaks were repeated in the drug formulation with polymer. The FTIR spectra indicated there is no chemical interaction between polymers and drug. However some additional peaks were observed in the spectra of formulation which may be due to polymers.

![Figure 1: FTIR spectra of diclofenac potassium (a) and drug polymer formulation (b)](image-url)
In vitro drug release studies

In vitro drug release profiles are used to ensure sustained release performance, reproducibility of rate and duration of drug release. Release studies were carried out in an open glass diffusion tube and hydrated cellophane was used as diffusion membrane. Figure 2 presents the drug release profile from GG/PVP polymer films. The result indicated that cumulative percentage of drug release decreased with increase in Guar gum content in the polymer matrix. The formulation GG/PVP 70/30 showed minimum cumulative drug release 70.84% is 5 hrs. The observed sustained release with increase in Guar gum concentration in polymer blend may be due to formation of GG/PVP miscible blend.

Kinetics of drug release

In order to understand the mechanism of drug release; in vitro release data were analyzed by Huguchi model & Koresmeyer-Peppas model. The plot of cumulative drug release as a function of square root of time is given in Figure 3. The curve shows good linearity with correlation coefficient 0.9565 to 0.9945 (Table 2). This indicated that the data is well fitted with Huguchi model and the mechanism of drug release was found to be diffusion controlled.\(^\text{10,13}\)

CONCLUSION

Physicochemical studies reveal that the distribution of drug is uniform in the polymer film. FTIR spectra of Diclofenac potassium and its formulation indicated that there is no chemical interaction between the drug and polymer. The release study indicated that the drug release rate was hindered as the Guar gum content increases in the blend. The drug release kinetic from GG/PVP blend was found to be controlled and follows non-Fickian mechanism. The formulation of drug with 70/30 GG/PVP showed minimum release rate.

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REFERENCE


<table>
<thead>
<tr>
<th>Weight ratio of GG/PVP</th>
<th>Higuchi model</th>
<th>Koressmeyer-Peppas model</th>
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<tbody>
<tr>
<td></td>
<td>Correlation coefficient, R</td>
<td>Diffusional exponent, n</td>
</tr>
<tr>
<td>70/30</td>
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<td>0.7222</td>
</tr>
<tr>
<td>60/40</td>
<td>0.9794</td>
<td>0.6071</td>
</tr>
<tr>
<td>50/50</td>
<td>0.9893</td>
<td>0.7882</td>
</tr>
<tr>
<td>40/60</td>
<td>0.9565</td>
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