Design and \textit{in vitro} evaluation of new drug-in-adhesive formulations of fentanyl transdermal patches

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Received February 9, 2004
Accepted October 19, 2004

The present research was designed to evaluate different matrix, drug-in-adhesive and reservoir formulations of fentanyl transdermal patches. The target was to design drug-in-adhesive patches (DIAPs); a full factorial design was used. Different types and amounts of liquid, pressure-sensitive adhesives (PSAs) were used and evaluated with respect to drug release and adhesive properties. A very simple but precise method, the simplified peel 180° test, was developed to measure and compare adhesive properties of transdermal patches. The results showed that release kinetics obeyed the square root of time or Higuchi model, indicating the diffusion controlled release mechanism. It was found that the amount of fentanyl needed for each 10 cm$^2$ three-days DIAP should be 3.3 mg. The respective amounts for reservoir and matrix patches were 2.5 and 5 mg. It was concluded that acrylic PSAs showed the best adhesion and release properties.

Keywords: fentanyl, transdermal drug delivery systems, patches, drug release

Fentanyl, with an analgesic potency of about 80 times that of morphine, was introduced into medical practice in the early 1970s for parenteral use in anesthesia. In 1991, transdermal reservoir patches (RPs) of fentanyl were approved for the treatment of chronic and cancer pains (1). Delivering of drugs into systemic circulation through skin has attracted a great deal of interest during the last couple of decades (2). Transport of compounds via skin is considered to be a complex phenomenon, which allows the passage of certain chemicals into and across the skin (3). The understanding of this complex phenomenon has lead to the development of transdermal drug delivery systems (TDDSs), in which skin serves as the site for administration of systemically active compounds such as fentanyl (4).

Among the various skin layers, stratum corneum (SC) is the rate-limiting barrier to percutaneous drug transport due to its desquamating ‘horny’ properties, comprising about 15–20 rows of flat, partially desiccated, dead, keratinized epidermal cells (5). Due to the lipid-rich nature of the SC layer (40% lipids, 40% protein, and only 20% water) and its

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low water content, transport of hydrophilic or charged molecules across SC is low while transport of lipophilic drug molecules such as fentanyl is higher due to their lipid miscibility with intercellular lipids around the cells in the SC layer (6).

Preparation of TDDSs consists of three basic designs: membrane control or RPs, matrix or monolithic patches (MPs), and DIAPs (see Scheme 1). Several factors should be considered before choosing an appropriate design for a particular compound: drug solubility, stability and release rate. As a rule of thumb, if a drug permeates or crosses the skin faster than desired, RPs can slow down or control the permeation (7). Alternatively, if a drug passes through skin at a slower rate than the patch releases it, MPs probably containing a suitable chemical penetration enhancer may suffice. These systems consist of a backing layer, a polymeric matrix, an adhesive and a protective liner (7, 8).

Scheme 1

In the early days of TDDS development, the worldwide mainstream was represented by the complicated structure of the reservoir type, in which the presence of a rate-controlling membrane was considered essential in order to achieve the drug release control. The very antithesis to the RPs are the so-called DIAPs, in which the overall function is achieved by concentrating the required functions into a single component of the adhesive polymer, which is definitely simple in structure (9). When the characteristics of these three different patches are compared (Table I), DIAPs and MPs are clearly superior to RPs in terms of patient compliance (7). It might also be expected, because of their simple

<table>
<thead>
<tr>
<th>Type</th>
<th>Structure</th>
<th>Formulation</th>
<th>Skin conformability</th>
<th>Size adjustment</th>
<th>Dose dumping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-in-adhesive or matrix patch</td>
<td>Simple thin layer</td>
<td>Complex</td>
<td>Good</td>
<td>Easy</td>
<td>Low potential</td>
</tr>
<tr>
<td>Reservoir patch</td>
<td>Complex multi-layer</td>
<td>Simple</td>
<td>Some discomfort</td>
<td>Difficult</td>
<td>Possible breakage of rate-controlling layer</td>
</tr>
</tbody>
</table>

*Italics* indicate superior characteristics.
structure, that DIAPs and MPs are superior from the commercial viewpoint in terms of the manufacturing process control, quality control and continuous product improvement. Moreover, the thinner construction of MPs and DIAPs may improve wearing comfort for the patient (10). However, drug formulations for MPs are more challenging to produce, particularly for those patches that incorporate the drug in the adhesive (11). The purpose of the present research work was to design new MPs and preferably DIAPs for fentanyl by regulating their drug release and adhesive properties.

EXPERIMENTAL

Materials

Micronized fentanyl was obtained from Diosynth (The Netherlands). Hydroxyl ethyl cellulose (HEC), ethyl cellulose (EC), and Carbomer 940 were from Clariant (Germany), Aqualon (The Netherlands), and 3V Sigma (Italy), respectively. Hydroxypropyl methylcellulose (HPMC K4M, HPMC K15M and HPMC K100M) and Eudragit® E were from Colorcon (UK) and Rohm (Germany), respectively.

Reference fentanyl RP formulation was Duragesic® 25 and 50 µg h⁻¹ (10 and 20 cm², respectively) from Janssen-Cilag (Belgium).

Control membranes, Cotran™, were donated by 3M (USA). Control membranes used in this study include: Cotran™ 9702 membrane, 50 µm, 9% vinyl acetate (VA), Cotran™ 9706 membrane, 100 µm, 9% VA, and Cotran™ 9728 membrane, 50 µm, 19% VA. These control membranes consist of ethylene vinyl acetate (EVA) containing 9% or 19% VA. Control membranes with a higher amount of VA have more drug permeability and also higher moisture vapor transmission rates (MVTR).

Cotran™ backing layers were also donated by 3M. Backings used in this study include: Cotran™ 9720 backing, 75 µm, polyethylene, Cotran™ 9722 backing, 75 µm, polyolefin, and Scotchpac™ 9723 backing, 42 µm, polyester-based laminates polyethylene – polyester. The backings have both a low MVTR and high oxygen transmission. These foster improved skin health by increasing moisture close to the skin to maintain skin hydration while allowing it to breathe.

The transferring PSA films, MA-31, MA-46, and HY-3 were gifts from Adhesive Research (USA) and 3M-1524 transferring PSA, 62.5 µm from 3M. Acrona® V 210, a 70% aqueous dispersion of carboxylated copolymer based on acrylate in combination with vinyl acetate, was kindly donated by BASF (Germany). Release liner, also known as peeling or protective liner, 3M Scotchpak™ 1022 liner, was donated by 3M.

Quadruple laboratory film applicator with a lateral guide plate and 4 thickness choices – 90, 170, 250, 500 µm, and a 90 mm gap width was purchased from Sandberg & Schneiderwind (Germany).

Support membrane (Spectra/Por® 7 with cut off 14000 Daltons) to fix patches in the dissolution vessel was purchased from Spectrum (USA). All solvents and reagents used were of analytical reagent grade and solutions were prepared with purified water (conductivity less than 1 µS cm⁻¹).
Preparation of fentanyl TDDS

Preparation of fentanyl RPs. – RPs consist of a backing layer, a drug reservoir, a rate-controlling membrane and an adhesive layer covered by a protective release liner. The active compound within RPs may exist as either a liquid or a gel or dispersed in a polymeric material. Full factorial design was applied by using three different concentrations of the gelling polymer (HEC 2, 3 and 4 percent), three types of the rate-controlling membrane with different percentages of VA content and various thickness, and solution and suspension formulations of fentanyl in its vehicle.

The rate-controlling membranes consisted of controlled caliper EVA microporous membrane films, which were heat-sealable to polyethylene and polyester backings. Different backing layers were also tested to find the perfect sealing matching our sealing device and its temperature. After sealing, the RPs were checked by the leak test in a vacuum desiccator.

The adhesive layer of the patches was hypoallergenic acrylate or silicone transferring film PSA. The composition of some polymeric mixtures used to prepare the RPs is shown in Table II.

Table II. Composition of some typical polymeric mixtures used for the preparation of fentanyl RPs

<table>
<thead>
<tr>
<th>Compound</th>
<th>R Sus 1</th>
<th>R Sol 2</th>
<th>R Sus 5</th>
<th>R Sol 8</th>
<th>R Sus 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>HEC*</td>
<td>8</td>
<td>8</td>
<td>–</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>HPMC K15M</td>
<td>–</td>
<td>–</td>
<td>8</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Glycerol</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.1</td>
</tr>
<tr>
<td>Water</td>
<td>0.3</td>
<td>0.2</td>
<td>0.3</td>
<td>0.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

R, Sus, and Sol denote reservoir, suspension, and solution, respectively. Amounts are expressed in mg (except for alcohol and purified water which are in mL).

* 8, 12, and 16 mg correspond to 2, 3, and 4% (m/V) polymer in the solvent, respectively.

Backin g layer and rate-controlling membrane were cut separately into circular pieces having a 3.6 cm diameter corresponding to a 10 cm² surface area. After applying an appropriate amount of gel containing fentanyl, their rims were sealed at 150 °C for 4–8 seconds by a heat sealing device developed in our laboratory. After cutting, RPs were protected using a protective release liner and finally each individual patch was packed in an opaque, white heat-sealed pouch. The pouch had laminated construction of bleached machine-glazed paper, low density polyethylene, aluminum foil (9 µm) and an inner low-density polyethylene heat-seal layer.

Preparation of fentanyl MPs. – MPs were prepared using a quadruple laboratory film applicator. Transdermal matrices of fentanyl were made using various concentrations of HPMC (K4M, K15M and K100M), ethyl cellulose, HEC, and Eudragit® E.
The accurate amount of drug per 10 cm² of patch was determined by varying the matrix thickness and appropriate percentage of fentanyl loaded in the dried matrix. The drug/polymer ratios used were between 1:10 and 1:20. Initially, according to the aforementioned ratio, drug and polymer were dissolved separately in alcohol and water. The two solutions were mixed and then glycerin or propylene glycol or another suitable plasticizer was incorporated. The mixture was then poured into the film applicator and spread on the backing layer at a constant rate of 1 mm/min with a constant wet thickness of 90, 170, 250 or 500 μm to obtain an acceptable amount of fentanyl per 10 cm². The films were dried in an oven at 60 °C for 15 min and then cut into a predetermined area containing an equivalent of 5 mg of fentanyl per each 10 cm². PSA sheets were then transferred onto the matrices and then the patches were protected using release liners, and finally each individual patch was packed in an opaque, white heat-sealed pouch as explained above. The composition of some polymeric mixtures used to prepare the MPs is shown in Table III.

**Table III. Composition of some typical polymeric mixtures used for the preparation of fentanyl MPs**

<table>
<thead>
<tr>
<th>Compound</th>
<th>M 1</th>
<th>M Sus 5</th>
<th>M Sol 8</th>
<th>M 9</th>
<th>M 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0.1</td>
<td>–</td>
<td>0.17</td>
<td>0.17</td>
<td>0.17</td>
</tr>
<tr>
<td>HEC</td>
<td>50</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>HPMC K15M</td>
<td>–</td>
<td>50</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ethyl cellulose</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>60</td>
<td>–</td>
</tr>
<tr>
<td>Eudragit® E 100</td>
<td>–</td>
<td>–</td>
<td>75</td>
<td>75</td>
<td>–</td>
</tr>
<tr>
<td>Glycerol</td>
<td>–</td>
<td>2.5</td>
<td>3.75</td>
<td>–</td>
<td>6</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>5</td>
<td>2.5</td>
<td>–</td>
<td>15</td>
<td>–</td>
</tr>
<tr>
<td>Dibutyl sebacate</td>
<td>–</td>
<td>–</td>
<td>15</td>
<td>–</td>
<td>6</td>
</tr>
<tr>
<td>Water</td>
<td>q. s.</td>
<td>q. s.</td>
<td>0.19</td>
<td>0.19</td>
<td>0.19</td>
</tr>
</tbody>
</table>

M, Sus, and Sol denote matrix, suspension, and solution, respectively. Amounts are expressed in mg, except for alcohol and purified water which are in mL. q. s. – quantum satis

**Preparation of DIAPs.** – The DIAPs were made of a flexible backing, a self adhesive controlled-release matrix containing fentanyl, and a release liner. The accurate amount of drug per 10 cm² of DIAP was determined by varying matrix thickness and appropriate percentage of fentanyl loaded in the dried DIAP. Aqueous methacrylic systems such as Acronal® and also cross-linked Eudragit® E were chosen for the preparation of the DIAPs. The latter is non-irritant and well tolerated by the skin and has two desired properties, release-rate control and self adhesion after cross linking with succinic acid (12). The adhesive matrix was prepared from an organic acid such as succinic acid and alcoholic solution of Eudragit® E. The composition of some polymeric mixtures used to prepare the DIAPs is shown in Table IV.
Macroscopic and microscopic examinations

In the case of suspension formulations, the presence of solid particles in the formulations was evaluated using a 8 × 60 Binoculars microscope (Zeiss, Germany). Evidence of any pin or defective sealing in RPs was evaluated by the leak test. This test was performed with a vacuum desiccator filled with methylene blue solution. Due to the importance of thickness in MPs and DIAPs, the thickness of the film in different areas was evaluated by a caliper or thickness measuring device.

Determination of solubility and analysis of fentanyl

Excess amounts of fentanyl were added to two different media, purified water and phosphate buffer solution (PBS), pH 7.2, and were agitated for 24 h at 23 ± 2 °C. The suspensions were filtered through a membrane filter of 0.45 μm to obtain a clear solution, and the concentrations of fentanyl were measured by a validated HPLC method as follows. Fentanyl content was analyzed using HPLC-UV (series 486 Waters, USA) at a detection wavelength of 230 nm. The column type was a reversed phase bondapack C_{18} (300 × 3.9 mm i.d., 10 μm particle size, Waters) and maintained at 40 °C. The mobile phase was 40:60 of ammonium acetate solution (1:100) and a mixture of methanol, acetonitrile, and glacial acetic acid (400:600:0.6). The pH of the mobile solution was adjusted to 6.6 ± 0.1 by dropwise addition of glacial acetic acid. The retention time and flow rate were 4.2 minutes and 2 mL min⁻¹, respectively (13).

In vitro release of fentanyl

Determination of the fentanyl release pattern in different RPs, MPs, and DIAPs and their comparison with reference RPs were carried out using a USP 26 (14) apparatus 5, paddle over disk, operating at 50 rpm in PBS with pH 7.2 equilibrated to 32 ± 0.5 °C. Due to adequate solubility of fentanyl corresponding to its concentration and provision of sink condition, 500 mL of PBS was used as dissolution medium. One patch was ap-

<table>
<thead>
<tr>
<th>Compound</th>
<th>DIA 3</th>
<th>DIA Sus 5</th>
<th>DIA Sol 8</th>
<th>DIA 11</th>
<th>DIA 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Acronal®</td>
<td>25</td>
<td>37.5</td>
<td>50</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Eudragit® E 100</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>DBS</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>4.5</td>
<td>11.2</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>5</td>
<td>7.5</td>
<td>10</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Succinic acid</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.9</td>
<td>3.46</td>
</tr>
<tr>
<td>Organic solvents</td>
<td>q. s.</td>
<td>q. s.</td>
<td>q. s.</td>
<td>q. s.</td>
<td>q. s.</td>
</tr>
</tbody>
</table>

DIA, Sus, and Sol denote drug-in-adhesive, suspension, and solution, respectively.  
q. s. – quantum satis  
Amounts are expressed in mg, except for alcohol and purified water which are in mL.
plied flat on the disk with the release surface facing up (effective area available to diffusion was 10 cm²) and a support membrane on top of it. This membrane was rehydrated by immersion in purified water 1 h before application. At predetermined time intervals, 5-mL samples were collected and immediately replenished with fresh medium. The samples were analyzed for their fentanyl content using the aforementioned HPLC method.

Adhesion properties

Peel adhesion 180° test. – One week after the preparation of TDDSs, they were cut into strips, 2.5 cm wide and 15 cm long, and conditioned for 24 h at 23 ± 2 °C and 50 ± 5% RH. The tests were performed with a tensile testing machine (Enrico Toniolo, Italy). The strips were applied to an adherent plate made of stainless steel, smoothed with a standard roller (2.04 kg) five times and pulled from the plate at a 180° angle at a rate of 300 mm min⁻¹ (15). The matrix had to peel cleanly from the plate, leaving no visually noticeable residue in order to show neat removal. The forces were expressed in cN per cm width of adhesive tape.

Thumb tack test. – One week after the preparation of TDDSs, the thumb was pressed lightly on a patch for about 5 seconds and then quickly withdrawn (16). By varying the pressure and time of contact, and considering the difficulty of pulling the thumb from the adhesive, it was possible to set a scoring as to how easily, quickly, and strongly the adhesive can form a bond with the skin. All the tests were simultaneously performed in a blind way on three samples.

Creep resistance test. – One week after the preparation of TDDSs, they were cut precisely into strips 2.5 cm wide and 6 cm long. 1.27 cm of the specimen was applied at the tab end in contact with an adherent plate made of stainless steel. The specimen was laid without pressure exactly parallel to the length of the test surface and smoothed using the aforementioned method. The prepared sample was placed in the shear adhesion rack to hold panels 2° inclined from the vertical so that the back of the panel formed an angle of 178° with the extended piece of sample. A 500 g weight was secured to the free end of the patch. The test was performed with an apparatus made in our laboratory according to PSTC-1 specification (15, 16).

Simplified peel adhesion 180° test. – This simplified adhesion peel 180° test is a combination of the creep resistance and peel 180° tests and was developed in our laboratory. The apparatus is similar to the creep resistance device but without any incline to the vertical axis. The major disadvantage of the creep resistance test is that it is time consuming, for example, for many moderate adhesives it may take long, even more than 2–4 hours. On the other hand, the major disadvantage of the peel adhesion 180° test is the need to use a tensile strength machine. These two problems have been solved in our simplified test. In practice, adhesive patches were cut into strips, 2.5 cm wide and 15 cm long, conditioned for 24 h at 23 ± 2 °C and 50 ± 5% RH. The samples, 6 cm of adhesive, were applied to an adherent plate made of stainless steel, smoothed using the aforementioned method and peeled from the plate at a 180° angle by a 500 g mass. In this test, the peeling time is reported in minutes.
Data analysis

The cumulative amount permeated through the membrane per unit area was calculated from the concentration of each patch in the dissolution vessel and plotted as a function of the square root of time (17).

Full factorial design of experiments was applied to investigate the effects of one experimental variable while keeping all the others constant (18).

Student’s t-test was performed to find any significant difference in the release rate between our TDDSs and the reference commercially available product.

RESULTS AND DISCUSSION

Macroscopic and microscopic examination

No evidence of crystal growth due to solvent loss was observed in the solution formulation. No pins or defective sealings were observed in RPs while they were evaluated by the leaking test. Using a lab coater with minimum spreading length of 30 cm and 1 m min\(^{-1}\) spreading speed, an average thickness of 130 ± 11 µm (mean ± SD) was obtained form 5 experiments. This method decreased the relative standard deviation of thickness to less than 8.5%. Several important parameters influence constant thickness. These include the minimum length and speed of film spreading, volume of polymer solution in the device reservoir, and the polymer solution viscosity. Low viscosity leads to »bleeding« of polymer solution beneath the film coater and high viscosity causes imperfect film layers.

In vitro release of fentanyl

Developing a discriminating dissolution medium using a proper dissolution apparatus is of tremendous value for a drug release study in TDDSs. The volume, pH, surface tension, and viscosity of medium are the most important parameters to be considered (9). Our analytical results showed that the solubility of fentanyl in water and PBS of pH 7.2 is 53 and 335 mg L\(^{-1}\), respectively. Therefore, both may provide the sink condition for fentanyl patches without any surface active agents. In these experiments, 500 mL PBS was selected as the discriminative dissolution medium since it created the sink condition.

Drug absorption into the skin generally, occurs by passive diffusion (19). The rate of drug transport across the SC follows Fick’s law of diffusion:

\[
J = \frac{dM}{Sdt} = \frac{D \Delta c K}{h}
\]

where \(dM/Sdt (J)\) is the steady-state flux across the stratum corneum, \(D\) is the diffusion coefficient or diffusivity of drug molecules, \(\Delta c\) is the drug concentration gradient across SC layer, \(K\) is the partition coefficient of the drug between skin and formulation me-
dium, and \( h \) is the SC thickness (19). In other words, the rate of drug transport depends not only on its aqueous solubility, but is also directly proportional to its oil/water partition coefficient, its concentration in the formulation vehicle, and the surface area of the skin to which it is exposed; it is inversely proportional to the SC thickness.

Plot of the cumulative amount of drug released per unit area (\( \mu g \ cm^{-2} \)) against the square root of time according to the Higuchi equation yields a straight line; the slope of the regression line represents the release rate (8). This formula is an integral form of the Higuchi equation (19):

\[
Q = (2ADC_s t)^{1/2}
\]

where \( Q \) is the cumulative amount of drug released per unit area of the matrix, \( A \) is the total drug concentration in the matrix, dissolved and undissolved, \( D \) is the diffusion coefficient of the drug in the matrix, \( c_s \) is the solubility or saturation concentration of the drug in the matrix, and \( t \) is time (19–21). There is another form of the Higuchi equation, its differential form, which leads to the calculation of the rate of release, \( dQ/dt \), at any time (8):

\[
\frac{dQ}{dt} = k \sqrt{t}
\]

where \( k \) is the release constant. Plot of \( dQ/dt \) against the reciprocal of the square root of time leads to a straight line.

**Drug release from RPs.** – Drug release data for 10 cm\(^2\) and 20 cm\(^2\) reference fentanyl RPs are summarized in Table V. Plotting the percent release of fentanyl from reference formulation versus time gives the pattern of release (Fig. 1). As it is shown in Fig. 1, the \( R^2 \) value for 10 cm\(^2\) reference RP is 0.08, showing that the release kinetics is not of zero order. Even considering the logical burst effect, and assuming 10 percent intercept, the \( R^2 \) value increased up to 0.5776, which indicates the non-linearity of the release profile.

![Fig. 1. Release of fentanyl from 10 cm\(^2\) (25 \( \mu g \ h^{-1} \)) reference formulation RPs (▲). Regression line without considering the burst effect (---, no intercept, \( R^2 = 0.08 \)); regression line with considering the burst effect (—, 10\% intercept, \( R^2 = 0.5776 \)). Each value represents a mean of three tests with the corresponding SD.](image-url)
Also $dQ/dt$ in Table V indicates that the rate of fentanyl release decreases with time for both 10 and 20 cm$^2$ reference RPs. Moreover, $Q$ values increase accordingly with the square root of time and depict a linear correlation indicating that fentanyl release kinetics from reference RPs obey the Higuchi model.

Two fixing methods, with and without the support membrane, were performed initially in the release studies for reference patches in order to show the effect of the support membrane on TDDS fentanyl release. Results showed that the support membrane had no significant influence on the release. Therefore, it was decided to perform all the release experiments with Spectra/Por® 7 with cut off 14000 Daltons as the support membrane to fix TDDS in the paddle over the disk apparatus.

Two main techniques are used to adjust fentanyl release in RPs: the first, which is more common and easier, changes the type and caliper or thickness of the control membrane, and the second changes the gel consistency, solution or suspension of the active

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>$10\ cm^2\ (25\ \mu g\ h^{-1})\ \text{RPs}\ \dfrac{dQ}{dt}$</th>
<th>$20\ cm^2\ (50\ \mu g\ h^{-1})\ \text{RPs}\ \dfrac{dQ}{dt}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>104</td>
<td>61</td>
</tr>
<tr>
<td>1</td>
<td>68</td>
<td>40</td>
</tr>
<tr>
<td>1.5</td>
<td>50</td>
<td>30.5</td>
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<tr>
<td>2</td>
<td>40</td>
<td>26.9</td>
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<td>4</td>
<td>21.38</td>
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<td>19.70</td>
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<td>15.57</td>
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</tr>
<tr>
<td>24</td>
<td>7.21</td>
<td>6</td>
</tr>
<tr>
<td>48</td>
<td>4.98</td>
<td>4</td>
</tr>
</tbody>
</table>

Fig. 2. Effect of different control membranes on the drug release of fentanyl RPs with the same gel formulation: ■ - Cotran$^{TM}$ control membrane 9728 ($R^2 = 0.8903$), ▲ - Cotran$^{TM}$ control membrane 9702 ($R^2 = 0.9812$), □ - Cotran$^{TM}$ control membrane 9706 ($R^2 = 0.9775$), and × - reference RPs ($R^2 = 0.9816$). Each value represents a mean of four tests with the corresponding SD.
substance, and sometimes both factors might be changed in the formulation (5). In Fig. 2, release of fentanyl in solution formulation was adjusted by applying different control membranes: Cotran® 9728, Cotran® 9702 and Cotran® 9706. It is shown that the amount of VA in the control membrane is critical for the drug release due to fentanyl hydrophobicity. The amount of Q reached its maximum value within 24 h using Cotran® 9728, while the amount of Q reached 60% within 72 h using Cotran® 9706. Due to high permeability and lipophilicity of fentanyl and according to the obtained results, 9% VA with 50 and 100 µm thick was used follows that both Cotran® 9728 and Cotran® 9706 are not appropriate control membranes since they cause either a fast release of fentanyl (Cotran® 9728) or its insufficient release (Cotran® 9706) within 72 h. However, Cotran® 9702 resulted in a desirable and complete release profile comparable to reference RPs within 72 h. Thus, it can be used as a reliable control membrane in RP formulations.

As it is shown in Fig. 2, the $R^2$ values are 0.9775, 0.9816, 0.9812 and 0.8903 for Cotran™ 9706, reference product (RP), Cotran™ 9702 and Cotran™ 9728, respectively. So, it shows that the reference product and three other formulations obey the Higuchi model.

The effects of changing the physical condition of formulations (solution and suspension) are shown in Fig. 3. When fentanyl was formulated in the solution form plus 2% gel the release from RPs was faster compared to reference formulation, whereas fentanyl in the suspension form plus 4% gel resulted in a slower release profile compared to reference formulation. Therefore, a 3% HEC fentanyl solution and a 2% HEC fentanyl suspension were made in order to adjust the release profile to the reference formulation. As shown in Fig. 3, both of these recent formulations resulted in a release profile comparable with reference formulation. Thus, the rate of drug release was dependent on both the solution and suspension forms of fentanyl formulation and its gel consistency.

As Fig. 3 shows, all the formulations obey the Higuchi (square root of time) model. The $R^2$ values are 0.9775, 0.9632, 0.9816, 0.9810 and 0.9342 for suspension and 4% gel, suspension and 2% gel reference RPs, solution and 3% gel, and solution and 2% gel, respectively.

**Drug release from MPs.** Different matrices were formulated by varying the concentrations of HPMC K4M, K15M and K100M, EC, HEC and Eudragit® E, whereas the drug
concentration was kept constant at 5 mg fentanyl per 10 cm². The important point is that in contrast to RPs where 2.5 mg fentanyl was required for 10 cm² to provide enough motor drive for drug diffusion, the MPs required twice as high a concentration per unit area, namely 5 mg fentanyl per 10 cm², in order to achieve the same motor drive.

As observed in Fig. 4, EC could not release fentanyl probably due to its hydrophobic properties. When dibutyl sebacate (DBS), was added to the formulation as a hydrophobic plasticizer, release of fentanyl reached the maximum ob 10% of the reference formulation after 72 h. Even replacing the plasticizer with a hydrophilic one, propylene glycol, the release of fentanyl increased to at most 30% of reference formulation, which is not enough. Therefore, although EC is a very good film forming polymer, it is not appropriate for fentanyl.

HPMC K15M and K100M were not suitable matrices due to their high viscosity. Application and spreading of these polymers with a lab coater was not possible and resulted in non-homogenous matrix layers. It was possible to make a homogenous film from HPMC K4M; however, the matrix thickness increased up to 600 µm, which is not acceptable with respect to patient compliance. Moreover, the release rate of fentanyl MPs formulated with HPMC K4M was rapid, which is not appropriate for a 3-day TDDS formulation (see Fig. 4).

As regards Eudragit® E, it was found that the amount of dry substance per square meter should be 50–70 g corresponding to a layer thickness of 50–70 µm. These thin layers, ready for application, are colorless, transparent and highly flexible. After preparing and transferring the PSA sheet, they should be immediately protected with a release liner, e.g., the 3M Scotch 1022 liner. It was also shown that DBS is not a suitable plasticizer due to the hydrophobic nature of fentanyl. However, using PG as a hydrophilic plasticizer combined with Eudragit® E resulted in a release profile of fentanyl from MPs comparable to its release pattern from reference RPs (see Fig. 4). Therefore, a mixture of Eudragit® E and PG can be an appropriate candidate matrix layer for the release of fentanyl from MPs. The $R^2$ values for all matrix formulations are close to that for the reference formulation showing that MPs obey the Higuchi model.

![Fig. 4. Comparative release of fentanyl from different MPs and reference RPs: ■ – M Sus 5 ($R^2 = 0.9258$), ▲ – reference RPs ($R^2 = 0.9816$), □ – M 9 ($R^2 = 0.9527$), ○ – M 15 ($R^2 = 0.9709$), and × – M Sol 8 ($R^2 = 0.8984$). Each value represents mean of four tests with the corresponding SD.](image-url)
Drug release from DIAPs. – The most important part of this research was based on formulating DIAPs, very thin and delicate patches. DIAPs are generally made of an organic adhesive mixture. Recently developed aqueous polymeric systems feature a number of advantages. Compared to organic solvents, water is more beneficial than any other agent because skin irritation and environment contamination are reduced. DIAPs were fabricated using two methods: a) crosslinking of Eudragit® E with succinic acid and a suitable plasticizer, b) using a liquid PSA such as Acronal® V 210.

As shown in Fig. 5 and Table VI, crosslinking of Eudragit® E did not yield adequate adhesion properties. It is generally assumed that the carboxyl groups of the cohesion promoter (e.g. succinic acid) enter into ionic interactions with the tertiary amino function of Eudragit® E. Two neighboring polymer chains can thus be linked with each other, which results in a modification of the system properties where the viscosity increases with the proportion of succinic acid without giving rise to the formation of a crosslinked solid body. The basic property of fentanyl may be the reason for inappropriate adhesion and inadequate crosslinking of Eudragit® E (22–24). However, Acronal® V 210 (as shown

![Fig. 5. Comparison of peeling strengths of different PSAs. Each value represents a mean of three tests with the corresponding SD.](image)

<table>
<thead>
<tr>
<th>Adhesive</th>
<th>Tack adhesive strength</th>
<th>Creep resistance time (min)</th>
<th>Peeling time (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA-31</td>
<td>+++</td>
<td>108</td>
<td>234</td>
</tr>
<tr>
<td>HY-3</td>
<td>++</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>MA-46</td>
<td>+++</td>
<td>174</td>
<td>375</td>
</tr>
<tr>
<td>3M-1524</td>
<td>+++</td>
<td>192</td>
<td>372</td>
</tr>
<tr>
<td>Acronal</td>
<td>+++</td>
<td>187</td>
<td>325</td>
</tr>
<tr>
<td>Eudragit E 100 and 9% succinic acid</td>
<td>–</td>
<td>Negligible</td>
<td>No adhering</td>
</tr>
<tr>
<td>Eudragit E 100 and 6% succinic acid</td>
<td>+</td>
<td>12</td>
<td>19</td>
</tr>
</tbody>
</table>

+++ aggressive, immediately after applying patch, ++ moderate, immediately after applying patch, + weak, after exerting considerable pressure, – no adhesion.
in Fig. 5 and Table VI) provided a reliable self-adhesive polymer to control the release of fentanyl from DIAPs. It should be mentioned that some rheological problems such as »bleeding beneath the lab coater« were observed, which required some viscosity increasing agents. Therefore, a mixture of 25 mg Acronal® and 12.5 mg HPMC K15 per patch can be an appropriate candidate DIAP for the release of fentanyl (Fig. 6). Respective $R^2$ values for DIA3, DIA Sol 8 reference RPs and DIA Sus 5 are 0.9676, 0.9812, 0.9816 and 0.9775. These data suggest that also these transdermal formulations obey the Higuchi model.

Adhesion properties

Adhesion plays a vital role for the effectiveness of transdermal patches. The adhesive properties of TDDSs are fundamental and the entire delivery surface of the patch has to maintain complete skin contact for the required period, 1 to 7 days or maybe even more, to ensure an efficient drug delivery. The adhesive polymers used in TDDSs are classified as PSAs and are defined as adhesives capable of bonding to surfaces with the application of light pressure (16). The adhesive properties can be evaluated in terms of »tack« and »peel«. Tack could be defined as the property that enables an adhesive to form a bond with the surface of another material upon brief contact under light pressure (11). Peel adhesion is the force required to peel away a strip of tape from a rigid surface (23). It is necessary to quantify the adhesive properties of the PSA used as the adhesive layer in these systems. Nowadays, there are several methods to determine the adhesive strength of PSAs, including the peel adhesion 180° test, thumb tack test, and creep resistance test (23, 24). A simple but precise method was developed in our laboratory by combining the peel adhesion 180° test and creep resistance test. The former needs a tensile strength apparatus that is not precisely controllable and the latter is a time-consuming method. In our method (modified or simplified peel 180° test), the peeling time needed to separate the patch from the plate is measured in minutes.

The obtained results of the peel adhesion 180° test revealed clear differences between the adhesions of various PSAs. MA-31 medical grade adhesive, a thermoplastic, moderately aggressive, acrylic copolymer PSA and 3M-1524 transferring film, a mild aggressive 62.5 µm acrylic copolymer PSA, showed better adhesion than the others. This is
due to their polymeric side chains structure. An alternative to high cross-link density is the use of grafted polymeric side chains, either alone or in combination with relatively low cross-link density. With this approach, reinforcement is achieved primarily through phase separation of the side chain within the continuous polymer network. The thickness of PSA in 3M-1524 transferring PSA is another reason for its better adhesion. The peeling strengths of different PSAs are shown in Fig. 5.

The tack properties and creep resistance results of different PSAs as well as the corresponding peeling time are reported in Table VI. The obtained results showed that MA-31, MA-46, 3M-1524 and Acronal® have the best adhesive properties to be used as PSAs in patch formulations.

The adhesion properties in DIAPs are more important than in the two other TDDSs, RPs and MPs, due to their incorporating a drug or some other polymeric substances in the adhesive layer. This may cause some problems in their adhesion properties. Polymer layers containing aminomethacrylate, Eudragit® E 100, sebacates and succinic acid permit DIAPs to compensate the effects of drugs and excipients on the adhesive properties.

CONCLUSIONS

The choice of an appropriate control membrane and gelling polymer in RP formulations are critical issues. The obtained data clearly demonstrate that the formulation of fentanyl RPs (according to the drug release pattern of the reference formulation of fentanyl RPs) was feasible with the drug in solution and in suspension using a Cotran® 9702 control membrane. The most important target in this research work was to develop new drug-in-adhesive and matrix formulations for fentanyl TDDS. It was clearly shown that acrylic PSAs, e.g. Acronal®, were able to control drug release as well as adhesive properties in DIAPs. It was also concluded that 50–70 g acrylic PSA per square meter created a film layer 50–70 μm thick, which can regulate the release of fentanyl from the matrix. The present studies have confirmed that DIAPs and MPs of fentanyl are able to compete with RPs due to the fact that the manufacturing processes for these transdermal patches are easier, faster, and cheaper. It was demonstrated that propylene glycol as plasticizer and release enhancer yields better film quality, flexibility, and conformability. Furthermore, a simple and rapid method (simplified peel 180° test) was developed for comparing and evaluating the adhesion properties of PSAs in TDDSs.

Acknowledgements. – The authors thank Mr. Assadi, Dr. Parnianpour and Dr. M. M. Sadeghi, members of the Board of Hakim Pharmaceutical Co., for their financial support. The authors also thank 3M for generously supplying various samples of different control membranes and backings.

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Dizajniranje i in vitro evaluacija transdermalnih flastera fentanila

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U radu su evaluirani različiti matriksni, adhezivni i spremišni ljekoviti oblici za transdermalnu primjenu fentanila. U dizajniranju adhezivnih flastera (DIAPs) upotrebljene su različite vrste i količine tekućih adheziva osjetljivih na tlak (PSAs). Evaluirano je oslobađanje ljekovite tvari i adhezivna svojstva. Za mjerenje i usporedbu adhezivnih svojstava transdermalnih flastera razvijena je vrlo jednostavna, ali precizna »metoda ljuštenja«. Rezultati su pokazali da kinetika oslobađanja slijedi kvadratni korijen vremena (Higuchi jev model), ukazujući na to da se ljekovita tvar oslobađa difuzijom. Pokazalo se da je za svakih 10 cm² DIAP-a za trodnevnu uporabu potrebno 3,3 mg fentanila. Ta količina je za spremišne i matriksne flastere iznosila 2,5, odnosno 5 mg. Najbolja adhezivna svojstva i oslobađanje fentanila bilo je iz akrilatnih pripravaka.

Ključne riječi: fentanil, transdermalni sustavi za isporuku lijekova, flasteri, oslobađanje ljekovite tvari

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