Preparation of celecoxib solid dispersions for dermal application: in vitro characterization and skin irritation test

S.M. Soliman¹, N.S. Abdel Malak*, O.N. El Gazayerly², A.A. Abdel Rehim¹

¹Department of Pharmaceutics, Faculty of Pharmacy, October 6 University, Egypt
²Department of Pharmaceutics, Faculty of Pharmacy, Cairo University, Kasr El Ainy Street, Cairo 11562, Egypt
*Correspondence: pharmnova@yahoo.com

The purpose of this work was to improve the dissolution and skin permeability characteristics of celecoxib. Solid dispersions (SDs) of celecoxib were prepared using PEG 4000, PVP K30 and HPβCD by the kneading method. The dispersions were characterized by, (DSC), (XRD) and in vitro drug dissolution. The solubility and dissolution of SDs were markedly increased as compared to plain drug. The kneaded dispersions showing high dissolution were incorporated in an o/w cream and evaluated for in vitro drug permeation through rabbit skin. The permeation rate of celecoxib were significantly increased in the case of SDs when compared to plain drug. The anti-inflammatory effect of celecoxib-PVP K30 cream was more effective in inhibiting rat paw edema when compared to celecoxib cream. Skin irritancy and histopathological investigation of rat skin revealed its safety thus confirming the advantage of improved pharmacological activity and safety of celecoxib when administered topically as solid dispersion with PVPK30.

Key words: Celecoxib – Solid dispersions – Skin permeation – Histopathology – Anti-inflammatory effect.

Celecoxib is a specific cyclooxygenase-2 inhibitor (COX-2) with no inhibition of cyclooxygenase-1 at therapeutic doses. Oral route is a well-accepted mean of administration but it leads to high variation in absorption and delayed onset of action of celecoxib (lag time 3-4 h) due to its low aqueous solubility (4 µg/mL)[1]. Recently, cardiotoxic effects associated with oral delivery [2] have suggested the need for developing alternate dosage forms that selectively deliver celecoxib to the upper and deeper layer of skin and offer many advantages over the upper and deeper layer of skin and offer many advantages over

I. MATERIALS AND METHODS

1. Materials

Celecoxib was obtained as a gift from Amoun Company (Egypt). Polyethylene glycol-4000 (PEG4000), polyvinylpyrrolidone K30 (PVP K30) and Hydroxypropyl-β-cyclodextrin (HPβCD) were obtained from Fluka AG, Buchs SG, Switzerland. Absolute ethanol and sodium lauryl sulfate (SLS) were obtained from Adwic, El-Nasr Pharmaceutical Chemical Company (Egypt). Millipore filter White soft paraffin, liquid paraffin, cetostearyl alcohol were of pharmaceutical grade, and all other chemicals were of analytical grade and were used without further purification. Celebrex capsules (100 mg celecoxib capsules, Pfizer, Egypt).

2. Preparation of celecoxib solid dispersions (SDs)

Solid dispersions of celecoxib were prepared using polyethylene glycol4000 (PEG4000) and polyvinylpyrrolidone K30 (PVP K30) at three different drug: carrier weight ratios of 1:1, 1:3 and 1:5. Solid dispersions of celecoxib were also prepared using hydroxypropyl-β-cyclodextrin (HPβCD) in 1:1 and 1:2 molar ratios [11, 14]. The calculated amounts of celecoxib and each of the aforementioned carriers at different ratios were mixed geometrically kneaded with 1:1 mixture of ethanol: water until obtaining a mass with a paste consistency, then dried in an oven at 50 °C. The dried mass was pulverized and sieved through a 180 µm sieve (size 80). The resulting celecoxib SDs were kept over anhydrous calcium chloride in a dessicator.

Ventura et al. [13] showed a positive effect of different cyclodextrins on the solubility and cutaneous absorption of celecoxib through human skin. The present study was focused to develop solid dispersions using PEG, PVP K30 and HPβCD in order to improve the solubility and dissolution rate of celecoxib. Dispersions showing optimum results were incorporated in an o/w cream. Skin permeability, anti-inflammatory effect and potential skin irritation were tested.
3. Evaluation of celecoxib solid dispersion

3.1 Solubility studies

The saturated aqueous solubility of celecoxib in distilled water was determined for the intact drug and drug solid dispersions. An excess amount of the sample to be tested was added to 5 mL of distilled water in stoppered vials and shaken reciprocally in a thermostatically controlled shaker (Precision scientific, United Kingdom) at 30 °C for 72 h to get equilibrium. The solution was removed from the shaker and filtered through 0.45 µm Millipore filter and the drug concentration in the filtrate was determined spectrophotometrically at 255.2 nm (Shimadzu, Kyoto, Japan) after appropriate dilution with distilled water. All experiments were run in triplicates.

3.2. In vitro dissolution studies of celecoxib solid dispersions

The dissolution profiles of the pure drug and its solid dispersions were evaluated using a USP dissolution apparatus II (Pharma. Test, Germany). An accurately weighted amount of each of the prepared SDs, equivalent to 10 mg of celecoxib, was placed in 1000 mL of distilled water and maintained at 37 ± 0.5 °C [13, 15]. The stirring paddle was rotated at a speed of 100 rpm. At predetermined time intervals (15, 30, 45, 60, 90, 120 min) aliquots of 5 mL of the dissolution medium were withdrawn and filtered using 0.45 µm Millipore filters for analysis and replaced with equal volume of fresh medium to maintain a constant volume. The concentration of celecoxib was determined spectrophotometrically at the predetermined λmax of 255.2 nm. The mean percentage of celecoxib dissolved was plotted as a function of time. All experiments were run in triplicates and the results were expressed as the mean values ± SD. The dissolution data were analyzed using the linear regression equations and to test for fitting to zero order, as the mean values ± SD. The dissolution data were analyzed using All experiments were run in triplicates and the results were expressed as the mean values ± SD. The dissolution data were analyzed using the linear regression equations and to test for fitting to zero order, as the mean values ± SD.

3.3. Differential scanning calorimetry (DSC)

DSC study was done to investigate crystalline status of celecoxib. About 2-4 mg of celecoxib, carriers and selected celecoxib solid dispersions were scanned at a rate of 10 °C/min on a Shimadzu DT-40 Thermal Analyser between 30 and 300 °C under dynamic nitrogen atmosphere. The DSC thermograms were recorded [16].

3.4. X-ray diffraction (XRD) studies

Powder X-ray diffraction patterns of celecoxib, carriers and selected celecoxib solid dispersions were recorded using a Philips X-ray diffractometer (PW1710) with a copper target at a voltage of 40 kV and a current intensity of 30 mA at a scanning speed of 1 °C/min.

4. Preparation of celecoxib solid dispersions cream

Selected celecoxib solid dispersions or plain drug were incorporated in an o/w cream equivalent to 2 % (w/w) of celecoxib. The cream was composed of 2 %w/w celecoxib, 30 %w/w emulsifying ointment and 68 % w/w water. The cream was formulated by dispersing an amount of celecoxib SDs (equivalent to 2 % celecoxib) or plain drug in the calculated amount of melted anionic emulsifying ointment composed of 30 % w/w emulsifying wax, 20 % w/w liquid paraffin and 30 % white soft paraffin. The calculated amount of slightly warmed distilled water was added to this mixture and stirred gently at room temperature until a cream was formed [17].

5. In vitro drug permeation studies through excised rabbit skin

5.1. Preparation of full excised abdominal rabbit skin barrier membrane

Ethical clearance was obtained from the institutional ethics committee at the Faculty of Pharmacy, Cairo University before the study. Rabbits were sacrificed with ether, the full thickness of rabbit skin was excised from the abdominal region, and hair was removed with an electric clipper. The subcutaneous tissue was removed surgically and the dermis side was wiped with isopropyl alcohol to remove adhering fat. The cleaned skin was washed with distilled water and stored in the deep freezer until further use. The skin was brought to room temperature and cut into circular patches when used [18].

5.2. In vitro permeation

Permeation of celecoxib from the prepared creams through the rabbit skin was carried out using static Franz glass diffusion cells (Micoette plus, Hanson Research, United States). These cells consist of donor and receptor chambers between which the rabbit skin membrane was positioned. The area for diffusion was 1.7 cm² and the receptor chamber volume was 14 mL. The receptor chamber was maintained at 32°C [19]. The receptor medium consists of 1 % SLS solution (w/v). Each cell contains a magnetic bar and was stirred at 100 rpm during the experiment. Weighed amounts of 0.5 g of the cream containing either celecoxib or SDs were evenly spread on the surface. Aliquots of 2 mL of the medium were withdrawn at 0.5, 1, 2, 3, 4, 5 and 6 h and replaced with equal volume of fresh medium to maintain a constant volume. The concentration of celecoxib was determined spectrophotometrically at the predetermined λmax of 255.2 nm [20] (Shimadzu, Kyoto, Japan). The mean percentage of celecoxib permeated across the membrane was plotted as a function of time. All experiments were run in triplicates and the results were expressed as the mean values ± SD (standard deviation).

5.3. Permeation data analysis

The average cumulative amount of celecoxib permeated through the skin per unit surface area (µg/cm²) was plotted as a function of time. The drug flux (permeation rate) at steady state (JSS) was calculated from the slope of the straight line. Permeability coefficient (KP) was calculated using the following equations:

\[ K_P = \frac{J_{SS}}{C_o} \]  
\[ E_r = \frac{J_{SS}}{J_{SS \text{ of control}}} \]

where \( C_o \) is the initial concentration of the drug. Enhancement ratio (Er) was calculated by dividing \( J_{SS} \) of the respective formulation by \( J_{SS \text{ of control}} \) [21, 22].

The coefficient of determination (R²), the amount of drug permeated after 6 h were also determined.

6. Anti-inflammatoryatory studies in rats

The study was conducted in accordance with the principles of Laboratory Animal care and was approved by the institutional ethics committee at the Faculty of Pharmacy, Cairo University. The anti-inflammatoryatory activity of the selected formula was carried out using the carrageenan-induced rat paw edema method developed by Winter et al. [23, 24] in albino rats. Male albino rats weighing 150-180 g were fasted overnight with free access to water and were divided into 4 groups each of 6 animals. The dorsal side of the rats was shaved 12 h before starting the experiments except in the control group. The first group (control) received carrageenan only without the drug. Second and third groups received an application of selected SD cream or celecoxib cream, respectively at 11.66 mg/kg dose level [25] on the shaved dorsal region of the animals half an hour before subplanter injection of carrageenan. The last group received oral treatment of commercial Celebrex capsule suspended in distilled water at a dose of 11.66 mg/kg by oral gavage. The animals were injected with carrageenan suspension in subplantar region of right hind paw. The paw edema volume was measured before carrageenan injection as well as...
after 1, 2, 3, 4, 5 and 6 h following the carrageenan injection using plethysmometer by the mercury displacement method [26]. The percentage inhibition of edema volume was calculated using the formula:

\[
\% \text{ inhibition} = 100 \times \left[1 - \frac{(A - x)}{(B - y)} \right]
\]

where A is paw volume after administration of carrageenan at time t, and x is paw volume before administration of carrageenan. B is the mean paw volume of control rats after administration of carrageenan at time t and y is mean paw volume of control rats before of carrageenan.

7. Correlation between in vivo anti-inflammatory activity and in vitro permeation results

In a trial, to correlate the permeation studies of the selected celecoxib formula with its anti-inflammatory activity. The cumulative amount of permeated drug at different time intervals (1, 2, 3, 4, 5 and 6 h) was taken as a parameter for the permeation studies, whereas the percentage inhibition in rat paw edema thickness (at the same time intervals) was taken as measure for the in vivo parameter anti-inflammatory activity. The results were plotted and the correlation coefficient was calculated.

8. Skin irritation test

The skin irritation test was carried out to determine any possible localized reaction of the selected SD celecoxib cream on the skin of male albino rats (150-180 g) according to the method described by Draize et al. [27]. The primary index (PII) was calculated by adding the edema and the erythema scores [27]. The animals were divided into three groups: the first group served as control (no treatment), the second group received 0.8 % v/v aqueous formalin solution as a standard irritant and the third group received the selected formula. A dose of 0.5 g of selected formula or 0.5 mL of formalin solution was applied on a 5 cm² area of the shaved dorsal side of the rats daily for three consecutives days [28]. The development of erythema and edema were monitored daily for 3 days.

9. Histopathological examination of skin specimens

After three days of application of celecoxib formulations, the rats were sacrificed and the skin samples from treated and untreated (control) areas were taken. Each skin sample was stored in 10 % (v/v) formalin saline solution. The skin samples were cut vertically in different sections. Each section was dehydrated using ethanol, embedded in paraffin for fixing and stained by hematoxylin and eosin and then examination was done through the light electric microscope (Nikon, Japan) fitted with cannon power shot G3 digital camera and compared with control sample.

II. RESULTS AND DISCUSSION

In the present work, solid dispersions of celecoxib with highly water soluble carriers namely PEG 4000, PVP K30 and HPβCD were prepared. Celecoxib was mixed with HPβCD in molar ratio of 1:1 and 1:2 whereas PEG 4000 and PVP K30 solid dispersions were prepared in the weight ratio of 1:1, 1:3, 1:5 by the kneading method. The results could be given under the following headings.

1. Solubility studies

The solubility of plain celecoxib in distilled water was 4.06 ± 0.42 µg/mL. Our results are in accordance with Gupta et al. [29] who stated that celecoxib is very hydrophobic in nature and achieved an equilibrium aqueous solubility of 3.46 µg/mL. Table I shows that all the prepared SDs showed a significant increase (p < 0.05) in celecoxib solubility with all different carriers and at different ratios used when compared to the plain drug. In addition, it was found that, as the amount of the carrier increased, the solubility of celecoxib increased. Our results are in accordance with Gupta et al. [29] who found that increasing the PVP concentration led to a significant increase in celecoxib solubility. Similarly, Punitha et al. [30] stated that increasing the urea concentration from 1:1 to 1.5 increased significantly the celecoxib solubility. Celecoxib solid dispersions prepared using HPβCD at 1:2 drug:carrier molar ratio and PVP K30 at 1:5 drug:carrier weight ratio gave 10-11 fold increase in celecoxib solubility when compared to the plain drug.

<table>
<thead>
<tr>
<th>Carrier used</th>
<th>Drug:carrier ratio</th>
<th>Saturated solubility (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain drug</td>
<td>-</td>
<td>4.06 ± 0.42</td>
</tr>
<tr>
<td>PEG*</td>
<td>1:1</td>
<td>14.36 ± 0.89</td>
</tr>
<tr>
<td></td>
<td>1:3</td>
<td>19.40 ± 2.38</td>
</tr>
<tr>
<td></td>
<td>1:5</td>
<td>17.11 ± 0.95</td>
</tr>
<tr>
<td>PVP K30*</td>
<td>1:1</td>
<td>14.23 ± 0.45</td>
</tr>
<tr>
<td></td>
<td>1:3</td>
<td>33.93 ± 1.07</td>
</tr>
<tr>
<td></td>
<td>1:5</td>
<td>44.23 ± 1.76</td>
</tr>
<tr>
<td>HPβCD**</td>
<td>1:1</td>
<td>28.23 ± 1.77</td>
</tr>
<tr>
<td></td>
<td>1:2</td>
<td>40.46 ± 4.73</td>
</tr>
</tbody>
</table>

*Weight ratio. **Molar ratio.

2. In vitro dissolution studies of celecoxib solid dispersion SDs

The dissolution pattern of pure celecoxib is illustrated graphically in all the dissolution figures for comparison. The dissolution rate of pure celecoxib was extremely low; only about 12.44 ± 0.71 % of drug was dissolved after 120 min. This might be attributed to the poor wettability and the hydrophobic nature of pure celecoxib, which exhibited tendency to form large aggregates during the run that caused the powder to float on the surface of the dissolution medium. The aggregation caused reduction in effective surface area of drug particles available for dissolution [31]. Figure 1 show the dissolution profiles of celecoxib from SDs prepared with different carriers at different ratios. The dissolution rate of celecoxib from all prepared SDs was significantly increased (p < 0.05) when compared to the plain drug. The increased dissolution rate of celecoxib in solid dispersions form can be attributed to several factors such as solubilization effect of the carrier, conversion to amorphous state, improved wettability of celecoxib, increased surface area due to decrease particle size and inhibition of particle aggregation. It was noticed also that increasing the drug: carrier ratio led to increase in the average percent of celecoxib dissolved. The results are in accordance with El Badry et al. [32], Chokshi et al. [33] and Kumar et al. [34] who found that the dissolution of poorly water soluble drugs increased by increasing the weight fraction of carriers in solid dispersion.

PVP K30 at 1:5 weight ratio and HPβCD at 1:2 molar ratio gave the maximum enhancement in dissolution of celecoxib when compared to all other ratios and to PEG4000. The dissolution of celecoxib from the solid dispersion prepared using PVP K30 at a ratio of 1:5 and HPβCD at a ratio of 1:2 were 7.6 and 6 fold higher than that of plain drug, respectively. This might be due to each single crystallite of the drug being encircled by the soluble carrier (PVP K30) which could readily dissolve and cause water to contact and wet the drug particle [35]. In addition, Sekikawa et al. [36] proposed that PVP in the medium might lower the surface tension and facilitated the wetting, thus, the dissolution of drug. These results were also in agreement with that found by Ulla et al. [37], who stated that, the dissolution of rofecoxib increased by using PVP in solid dispersions. Complexation, partial amorphization of the drug and its improved wettability in the presence of HPβCD were factors that influenced the dissolution profile of celecoxib in the solid dispersions prepared using HPβCD [14]. According to the values of the coefficient of determination (R²), the mechanism of drug dissolution was defined. It was found that all
512
of celecoxib solid dispersion at 1:5 ratio revealed the disappearance of the characteristic peak of the drug. These suggest two possibilities: amorphous precipitation of the drug and its better solubilization in the carrier. A shallow endotherm was seen at 158.8 °C in celecoxib solid dispersion with HPβCD at 1:2 molar ratio, indicating partial amorphization of the drug due to drug HPβCD interaction. In addition, a characteristic endotherm was seen at 271.3 °C. This endotherm was not observed in the thermogram of celecoxib. This may be due to an interaction between CXB and HPβCD promoted by the heating process in the DSC operation. This is in accordance of Ahsan et al. [38] who explained this on the basis that melting of one of the components can facilitate interaction in of drug and carrier. Our results are also in accordance to Nagarsenker and Joshi [14] who found similarly a characteristic endotherm in the range of 250 to 290 °C in all celecoxib HPβCD solid dispersion. They attributed this peak to heat induced interaction of the drug with HPβCD which resulted in the formation of an association form exhibiting different thermal behavior than CXB. Ventura et al. [13, 39] detected the appearance of new peak at 250 °C for celecoxib dimethyl βCD solid dispersion prepared by freeze drying, this was attributed to the formation of a new solid phase, which melts at higher temperature with respect to the free drug.

4. XRD studies
XRD studies were done to investigate the crystalline status of the samples. The peak position (angle of diffraction) is an indication of a crystal structure, and peak heights are the measures of samples crystallinity [40].

Figure 3 shows the XRD diffractograms of plain celecoxib, carriers and their solid dispersions characterized by high improvement in both solubility and dissolution (celecoxib: PVP K30 at 1:5 weight ratio and HPβCD at 1:2 molar ratios). The XRD data are in good agreement with the results established by DSC measurements.

The diffractogram of celecoxib exhibited a series of intense peaks at 2θ 0-60° the most indicative are 5.3, 10.7, 11.0, 13.0, 14.8, 16.0, 17.9, 19.6, 21.5, 22.4, 23.5, 25.4, 29.5 and 34.9°. The respective signal heights were in the order of 1631.40, 1341.52, 353.65, 686.52, 2608.20, 5094.54, 856, 1568, 6548, 1311, 654, 985.97, 2307.99 and 771 cts, respectively, which were indicative of the high crystallinity. HPβCD exhibited peaks at 9.37 and 18.46°70° with respective signal heights of 1306 and 2710 cts. PVP exhibited also two peaks at 10.9 and 20.73° of 2518 and 2194 signal heights, respectively. On the other hand, solid dispersion of HPβCD showed peaks at 10.67, 14.77, 16.11, 19.6 and 29.5 ° of 648, 721, 1527, 1392 and 468 cts, respectively.
5. Evaluation of the prepared cream containing celecoxib SD

5.1. In vitro skin permeation studies

In vitro drug permeations were carried out for the selected celecoxib SDs after formulation into creams to evaluate the ability of SDs to increase celecoxib permeation through excised rabbit skin (1.7 cm²) over a period of 6 h in 1% SLS solution (w/v). The results of the cumulative amount permeated per unit area of celecoxib as plain drug, celecoxib:PVP K30 at 1:5 weight ratio or celecoxib:HPβCD at 1:2 molar ratio solid dispersions were illustrated graphically in Figure 4.

Both celecoxib: PVP K30 and celecoxib: HPβCD solid dispersions increased the celecoxib permeation from creams through excised rabbit skin when compared to celecoxib cream (p < 0.05) but the effect was
more pronounced in case of PVP K30 solid dispersion, this may be due to PVP increased the drug solubility and thermodynamic activity in the vehicle which leads to increased permeability of the drug.

The permeation parameters were calculated and presented in Table III. The presence of PVP K30 solid dispersion in the cream, increased the JSS by about 2.79 times when compared to plain drug. This could be explained on the basis that PVP might possess a penetration enhancing effect. This might be also attributed to the decrease in the particle size of the drug, the increase of its wettability and the prevention of its aggregation by complexation with PVP which caused enhanced dissolution rate. It was previously found by El-Badry and Fathy [32], that the percutaneous absorption of meloxicam was improved by complexation with PVP. From the previous results it can be concluded that the overall in vitro permeation was strongly correlated with the solubility and dissolution studies. Similarly, Saleem et al. [43] found that PVP enhanced the permeation flux of ketoprofen when compared to plain drug, and the in vitro permeation results were also correlated to the solubility and dissolution studies. Based on the above results celecoxib:PVP K30 cream was chosen for, anti-inflammatory studies, in vitro in vivo correlation and skin irritation test in rats.

5.2. Anti-inflammatory studies in rats

Figure 5 shows that the anti-inflammatory activity of celecoxib-PVP K30 cream exhibited rapid onset in reduction of paw edema and was significantly (P < 0.05) higher than celecoxib cream at 4 and 6 h (percentage reduction of rat paw edema of 35.82 ± 4.3 % and 37.68 ± 2.1 % versus 19.89 ± 3.0 % and 24.76 ± 3.8 %, respectively) and higher than Celebrex capsule at 4 h (respective values of 35.82 ± 4.3 % versus 28.40 ± 5.1 %) but did not significantly differ from Celebrex capsule at 6 h (P > 0.05). The enhanced anti-inflammatory effects of celecoxib-PVP K30 cream could be due to the improvement of aqueous solubility and dissolution of celecoxib by using solid dispersion. Our results are in accordance with Muralidhar et al. [44] who compressed Celecoxib:PVP 1:4 solid dispersion into tablets and gave them orally to rats. It was found that the anti-inflammatory activity of celecoxib was relatively higher with more rapid onset in the case of solid dispersions when compared to celecoxib pure drug, this was attributed to the higher rates of dissolution and absorption of celecoxib from these systems.

5.3. Correlation between in vivo anti-inflammatory activity and permeation results

Figure 6 shows the correlation between the in vitro permeation of celecoxib (cumulative amount of celecoxib permeated, µg/cm²) and its in vivo efficacy (% inhibition in rat’s paw edema thickness) at the specified time intervals.

Correlation showing a linear function after 1 to 6 h was obtained. A statistical test was adopted to compare the correlation coefficient to zero (test for the significance of the correlation coefficient). The test is a t test with n-2 degrees of freedom of the form [45]:

\[ t = r \sqrt{n-2} / \sqrt{1-r^2} \]  

Eq. 4

The calculated t values was 4.7 for celecoxib-PVP K30 cream of permeation and its in vivo efficacy correlation. Since this value is higher than the corresponding tabulated t value (2.78) at 5 % level, it is concluded that the correlation coefficient (r) is significantly different from 0 and the cumulative amount permeated (µg/cm²) of celecoxib and the percentage inhibition in rat paw edema are strongly positively correlated.

5.4. Skin irritation

The skin irritation test was performed to confirm the safety of the selected celecoxib-PVP K30 cream. Draize et al. [27] mentioned that a value of the primary irritancy index (PII) < 2 indicates that the applied formulation is non-irritant to human skin. Therefore, celecoxib-PVP K30 cream was considered to be non-irritant as PII < 2 and the results are illustrated in Table IV. Our results are in accordance with Mittal et al. [46] who prepared transdermal patches of nitrendipine using PVP K30 and proved the absence of skin irritation as suggested by skin irritation score of 1.16 (< 2.00) under Draize score test. It was previously reported that undiluted PVP K30 was not a dermal irritant or sensitizer in clinical tests and is safe for use in cosmetics [47].

5.5. Histopathological examination

Histopathological examination of celecoxib-PVP K30 cream
treated and control rat skin was performed using a Nikon light microscope (Japan) and illustrated in Figure 7. The photomicrographs of control rat skin (untreated) group showed normal skin with well defined epidermal and dermal layers as shown in figure (Figure 7A).

While the second group (formalin solution as standard irritant), the photomicrograph showed inflammatory cells infiltration and blood capillaries dilatation in the dermis (Figures 7B and 7C). When the skin was treated with the selected celecoxib-PVP K30 cream for 72 h, the dermis did not show any inflammatory cell infiltration. There was no histopathological alteration or apparent signs of skin irritation (erythema and edema) observed on skin specimens indicating the absence of any skin irritation as a consequence of celecoxib-PVP K30 cream treatment (Figure 7D). These results indicated that the developed celecoxib-PVP K30 solid dispersion is safe for skin delivery of celecoxib.

* The solubility, dissolution and permeability of celecoxib were significantly enhanced by using solid dispersions. Celecoxib-PVP K 30 in 1:5 weight ratio solid dispersion incorporated into cream showed the highest drug permeation through rabbit skin and higher anti-inflammatory activity when compared to cream containing plain celecoxib. The in vivo anti-inflammatory effect was perfectly correlated with the in vitro permeation results. Skin irritancy and histopathological investigation of rat skin revealed the safety of the formulation for dermal use. The results suggested that the developed celecoxib-PVP K30 cream has great potential for enhanced skin permeation of the drug.

REFERENCES

20. Jain S.K., Gupta Y., Jain A., Bhol M. - Multivesicular liposomes...
Preparation of celecoxib solid dispersions for dermal application:
in vitro characterization and skin irritation test
S.M. Soliman, N.S. Abdel Malak, O.N. El Gazayerly, A.A. Abdel Rehim

ACKNOWLEDGEMENT

I would like to express my deep thanks and sincere gratitude to Dr. Samia A. Nour, professor of Pharmaceutics, Faculty of Pharmacy, Cairo University for her support and her effort in revising the paper. Also the authors are thankful to Dr. Noha Nagah, Lecturer of Pharmacology, Cairo University, for performing the rat paw edema experiment.

MANUSCRIPT
Received 10 May 2011, accepted for publication 11 July 2011.