RESEARCH ARTICLE

Inhibition of Crystallization in Highly Loaded Drug Bilayer Topical Patch using Lipid-Based Cosolvent

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ABSTRACT

A topical patch with highly loaded drug may lead to instability by forming recrystallization and causing gritty and dry patch also has implications for the rate of drug absorption through the skin and patch adhesion strength. The idea of keeping the drug to be molecularly dispersed will prevent the drug from being recrystallized. In this research, the lipid-based cosolvent was used to dissolve the drug as well as to keep the drug molecularly dispersed. Sodium diclofenac was used in this research as a drug model to be loaded into the topical patch. The current study aimed to develop topical patch formula and to evaluate the effect of using lipid-based cosolvent in preventing recrystallization. The patch was prepared using solvent casting method. The evaluation of the effect of lipid-based cosolvents in preventing drug recrystallization was carried out using x-ray diffraction method. The result showed that the addition of lipid-based cosolvents to the highly loaded sodium diclofenac topical patch formulation was able to prevent crystallization after storage at room temperature for six days.

Keywords: topical patch, crystallization, lipid-based cosolvent, sodium diclofenac

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INTRODUCTION

Transdermal delivery has become one of the most favourable methods for drug delivery system. Drugs administered by transdermal delivery systems able in avoiding the gastrointestinal tract, and thus avoid hepatic first-past metabolism and gastrointestinal tract irritation. Drug delivery through the skin also favourable for its direct delivery to local tissue under the skin as well as able in maintaining an effective rate of drug delivery over time and the benefits of a passive delivery system and diffusion. These benefits can be achieved by using a patch delivery system. Especially for topical administration of nonsteroidal anti-inflammatory drugs (NSAIDs) which widely accepted as a treatment for acute musculoskeletal conditions as they can provide good levels of pain relief with an improved efficacy and acceptability[1–3]. However, patches also have drawbacks that could potentially reduce the effectiveness of their use, such as the formation of drug recrystallization, which has implications for the rate of drug absorption through the skin and patch adhesion strength[4,5]. Therefore, the presence or absence and the degree of drug crystallinity must be controlled to guarantee the quality of patches[6,7]. The process of drug crystal formation does not occur immediately, causing the occurrence of recrystallization not to be detected immediately after the product is manufactured[8–10].

The limited area of the patch used on skin also limits the capacity of each patch sheet to carry the drug for a single use. Therefore, the drug dose incorporated into the patch must be able to be accommodated in each patch sheet and remain molecularly dispersed. A large dose loading in a patch sheet is one of the factors that can trigger crystallization of the active substance. A large dose load can cause the active substance to exceed the solubility capacity of the matrix so that the drug is saturated in the patch matrix and can lead to crystal formation[11–13]. The cause of crystal formation is not only due to saturation in the patch but can also be due to the low solubility properties of the drug[4,14,15]. Thus, one of the efforts to minimize the risk of drug crystallization is to increase the solubility of the active substance and or keep the drug molecularly dispersed. For this purpose, a formulation strategy that can be applied is to increase the solubility of the drug using cosolvent additives incorporated in the patch. A cosolvent system is a combination of several solvents that can increase drug solubility[16–18]. The solvent used can be a lipid-based solvent considering that the drug used is lipophilic. Lipid-based cosolvents can be a combination of oils with the advantage of being Generally Recognized as Safe (GRAS). In addition to oil, surfactants are also added to produce a stable cosolvent while facilitating the incorporation of the drug with the hydrophile patch matrix polymer.

In this study, the effect of lipid-based cosolvents combined with surfactants on the crystallization of active substances in topical pacts loaded with high-dose drugs will be observed. The model drug used is sodium diclofenac which

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Table 1: Bilayer patch loaded with cosolvent and sodium diclofenac

Parch Materials		% w/w	Sodium diclofenac in cosolvent (mg)			
			F1	F2	F3	F3
First layer	Pectin	0.5	-	-	-	-
	Propylene glycol	2.5				
	Glycerine	2.5				
	Aquades	Ad 100				
Second layer	CMC Na	2	60	120	60	120
	PVA	2				
	Propylene glycol	2.5				
	Glycerine	2.5				
	Aquades	Ad 100				
	Cosolvent		1 mL	2 mL	-	-

is a crystalline compound and is included in Biopharmaceutical Classification System class II, which is low solubility but has good permeability[19]. The cosolvents used in this study consisted of lipophile ingredients and were combined with surfactants. Attempts to prevent drug crystallization in patches that have been reported are the addition of crystallization inhibitors such as polyvinylpyrrolidone (PVP) conducted by[20] and the use of nanoparticles studied by[21]. In this study, the patch used is a double-layer patch, which is a patch with two different layers between those that function as a drug matrix and those that function as an adhesive.

MATERIALS AND METHODS

Materials

The lipid-based cosolvent was prepared using castor oil was bought form Subur Kimia Jaya Semarang, Indonesia, polyethylene glycol 40 hydrogenated castor oil (PEG 40 HCO), Span 80, polyethylene glycol 400 (PEG 400), propylene glycol, glycerine was produced by Clariant and purchased from the distributor Subur Kimia Jaya Semarang, Indonesia. The polymers were pectin (Tokyo Chemical Industry), sodium carboxymethyl cellulose (CMC Na) and polyvinyl alcohol (PVA) (BASF®). Sodium diclofenac in compliance with BP/USP was produced by Xi'an Lyphar Biotech Co. Ltd and purchased from local chemical company in Malang East Java.

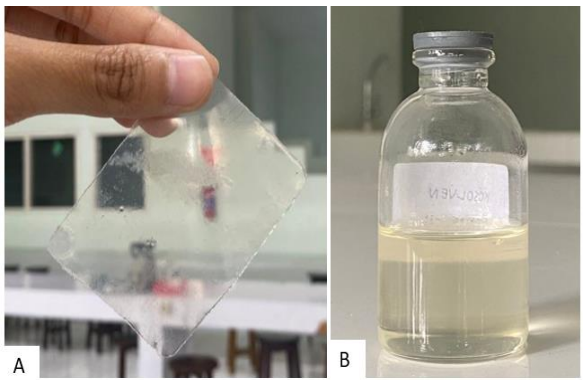

Figure 1: A) Bilayer patch, B) Cosolvent

Table 2: Swelling index measurements

	Minutes	*Swelling index* (%) Mean ± SD*
F1	0	0
	5	-
	10	-
F2	0	0
	5	-
	10	-
F3	0	0
	5	60,33 ± 0,059
	10	-
F4	0	0
	5	243,37 ± 0,129
	10	-

*n= 3 replications

Table 3: Patch weight uniformity and thickness

	Weight uniformity (g) Mean±SD*	Thickness (mm) Mean±SD*
F1	2,7 ± 0,0216	0,3 ± 0,0144
F2	2,6 ± 0,0118	0,3 ± 0,0144
F3	1,8 ± 0,0101	0,3 ± 0,0144
F4	2,1 ± 0,0107	0,3 ± 0,0144

*n= 3 replications

Methods

Preparation of Cosolvent System

This study used a lipid-based cosolvent consisting of an oil phase, namely castor oil, Span 80, PEG 40 HCO and PEG 400 as surfactants. The concentration of each composition used in this study cannot be specified due to the patent filing period by the author. In general, the castor oil range between 30-35 %, and the rest was surfactant mixture at certain ratio of each material. For certain circumstance anyone still can contact us for explanation of the cosolvent compositions. All materials were mixed in a glass beaker and then stirred using a magnetic stirrer at 500 rpm for 20 minutes at 40 ^{O}C. After the mixture has reached room temperature, the cosolvent can be stored in a vial until the next use.

Solubility Test of Diclofenac Sodium in Cosolvent System

Solubility testing of sodium diclofenac in cosolvents was carried out using the saturation shake-flask method[22]. This test was conducted to confirm the solubility level of sodium diclofenac in cosolvenes and confirm that it was able to enhance the solubility of sodium diclofenac. 1 mL of cosolvent in the vial was added to sodium diclofenac until saturation which was marked by the formation of a precipitate. Addition of diclofenac sodium was carried out periodically until saturation while shaking using an orbital shaker for 24 hours at 100 rpm continuously. After another 24 hours, centrifugation was carried out at 3000 rpm for 10 minutes. The supernatant then analyzed using Shimadzu 1700 UV-Vis spectrophotometer at a wavelength of 278 nm (based on the results of maximum wavelength determination on the device).

Patch Loading Capacity Optimization

In this study, a bilayered patch was prepared consisting of a first layer which is a polymer matrix layer functioning as an adhesive layer and a second layer which is a polymer matrix layer functioning to load the drug. The patch was designed to be 4.5x6.5 cm in size for each strength of diclofenac sodium for single use. This size is based on the average commercially available patch. The loading capacity of the patch was determined to determine the optimum volume capacity of cosolvent that could be loaded into the patch of this size while maintaining its physical properties. Cosolvents of 1, 2, 3, 4, 5 mL each were added to the equivalent patches of size 4.5x6.5 cm and visually observed whether there was any permeation of cosolvents from the patch system or not. Observations were made visually using oil paper.

Bilayer Patch Preparation

Patches were prepared using the solvent casting method[23]. The patch composition used is listed in Table 1, in which each patch unit cons00000ists of two layers (first layer and second layer).

The first layer was made by dissolving pectin in distilled water. Subsequently, propylene glycol and glycerin were added and distilled water was added until reached a volume of 40 mL while stirring using a magnetic stirrer for 15 minutes. The solution was then placed in a Petri dish and dried in an oven at 40 ^{O}C for 15 hours. After the first layer dried, the second layer patch was prepared. The polymer solution for the second layer was prepared by dissolving CMC Na in distilled water until a concentration of 2% was obtained. In another container, PVA was dissolved in 100 mL distilled water. The CMC Na and PVA solutions were then mixed at a volume ratio of 1:5 and stirred until homogeneous. Then, propylene glycol and glycerin were added and homogenized using a magnetic stirrer. The second layer mixture was then added with distilled water until it reached a volume of 40 mL while stirring using a magnetic stirrer at 80 ^{O}C. In another container, sodium diclofenac solutions of various concentrations in cosolvents (Table 1) were prepared and added to the second layer polymer solution at room temperature. Based on the results of solubility study the amount of cosolvent used was 1 mL for every 60 mg of diclofenac sodium. Next, the mixture was poured over the dried first layer patches and dried using an oven at 40 ^{O}C for 15 hours.

Swelling Index

Patch strips sized 4x4 cm were weighed and recorded as initial weight (W_0). It was then placed in a petri dish containing 10 ml of distilled water and weighed at each time point. Weighing of the patch was carried out at 5, 10, 15, 20, 25, and 30 minutes. The weighing result was designated as (Wt). Swelling Index (S%) was obtained from the last weighing where the patch was still intact. Swelling index (S%) was calculated as follows = ((Wt - W_0) / W0) x 100%[24].

Folding Endurance

The 2x2 cm patch strips were folded repeatedly in the same position until the patch tore. The folding endurance result is calculated based on the number of folds that can be performed without damaging the patch piece[24].

Patch Weight Uniformity Test

Three different points on the patch area of each dried batch were determined. At these points, the patches were cut to a size equivalent to 4.5x6.5 cm and weighed. The results of the weighing were then calculated for standard deviation[24].

Patch Thickness Test

Three different points on the patch area of each batch of printing that had dried were determined. At these points, the patches were cut to a size equivalent to 4.5x6.5 cm and the thickness was measured using a caliper[24].

Adhesion Test

Patch adhesion test was conducted using rolling ball tack test. Patches were arranged on a flat surface (laboratory work table) forming a 30 cm long track adjacent to the end of the ball track on the device. The patches were placed with the adhesion surface facing up (not attached to the base). Then, a stainless steel ball with a diameter of 13.5 mm was rolled on the track of the device which has a 30º track slope. When the ball was rolled, the distance traveled by the ball was measured with a ruler[25].

X-ray Diffraction (XRD)

The drug in the patch was analyzed for its degree of crystallization using XRD at 2θ with a range of 10º -70º.

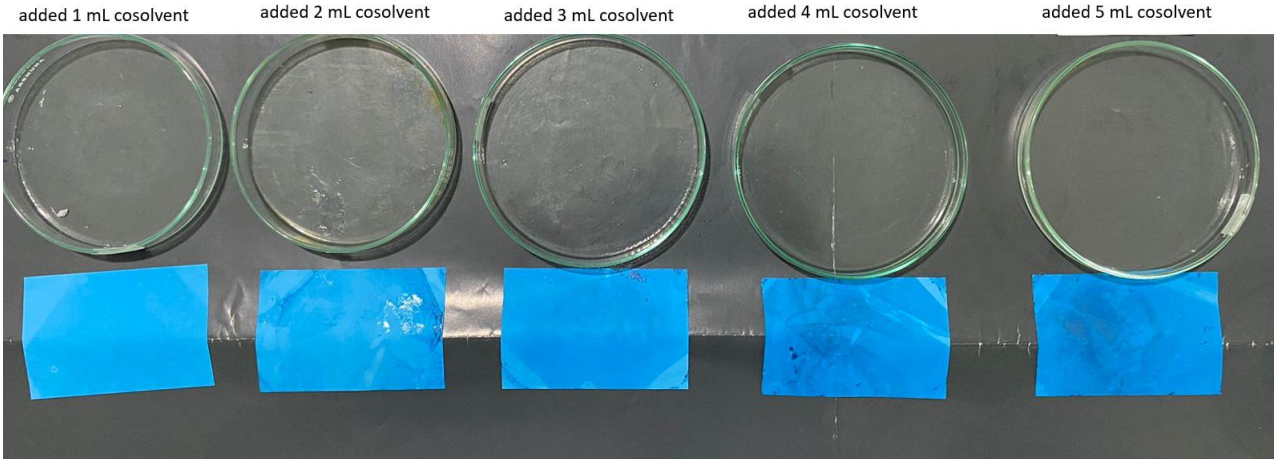

Figure 2: Visualisation of patch added with cosolvent for loading capacity determination. Patches incorporated with 3 mL of cosolven showed maximum capacity as they started to show the cosolvent component absorbed by the oil paper but still no leakage from the matrix. The volume of 3 mL will be used as the maximum limit of cosolvent that can be used for the next formulation

The X-ray wavelength used was 1.54 (Sa'adon et al., 2021). The samples were analyzed twice, immediately after the patch was made (freshly prepared) and six days after storage at room temperature. Patch formulas containing sodium diclofenac in cosolvents (F1 and F2) were compared for degree of crystallization to patches containing sodium diclofenac without cosolvents (F3 and F4).

RESULTS AND DISCUSSION

Based on the solubility test results of diclofenac sodium in cosolvents, it is known that the solubility of diclofenac sodium in the cosolvents used in this study is 59.98 mg/mL. This amount is much greater than its solubility in polar solvents such as water, which is 20.4 mg/mL[26]. The high solubilization capacity by the cosolvent is expected to keep diclofenac sodium molecularly dispersed in the patch so as to inhibit drug crystallization during storage. The resulting bilayer patches and cosolvents are as shown in Figure 1. The resulting patches are elastic and transparent homogeneous in structure. Likewise, the cosolvents were homogeneous.

The results of the patch loading capacity test show that each patch equivalent to 4.5x6.5 cm in size can accommodate 3 mL of cosolvent liquid. More than this volume, the cosolvent seeped out of the patch matrix (Figure 2). Loading capacity is important to ascertain the amount of drug that can be dissolved in the cosolvent and incorporated in the patch.

The results of the swelling index test on the four formulas (Table 2) showed that the formula combined with cosolvent (F1 and F2) had a poor swelling index compared to the formula without cosolvent (F3 and F4). Yet, F3 has higher swelling index compared to F4. Patch formula containing cosolvent cannot absorb liquid and dissolve immediately. This is reasonable because the cosolvents contain surfactants that support the polymer matrix to dissolve immediately. Meanwhile, the formula without kosolven can absorb liquid in the first 5 minutes but began to dissolve in the tenth minute. This result is acceptable if the intended use of the topical patch is not to absorb liquids, for example as a wound dressing. If wound dressing is desired, a more lipophilic polymer component can be used.

The folding endurance test results show that the four formulas have excellent flexibility with repeated folds reaching >300 folds. Patch flexibility reflects that the patch will not tear easily during use. Good patch elasticity is obtained by the presence of plasticizers in the patch formula, which are propylene glycol and glycerin.

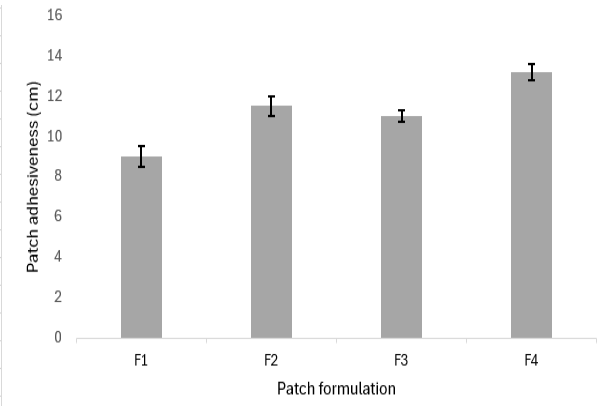

Figure 3: Patch adhesiveness measured using rolling ball tack test

The results of the patch weight and thickness uniformity test showed that the patches had a homogeneous mass. This indicates that the manufacturing process is consistent. The test results are shown in Table 3. In addition, thickness also affects the consistency of drug release. Homogeneous thickness ensures that the drug diffusion process from the patch to the skin is consistent.

Another physical property test that supports the effectiveness of patch use is the ability to adhere to the surface. Based on the test method used in this study, patch adhesion is considered good if the distance traveled by the stainless steel ball is less than 25 cm. The results of the adhesion test are shown in Figure 3. The distance travelled indicates the ability of the adhesive layer to restrain the rate of motion of the stainless-steel ball. The shorter the travel distance of the stainless-steel ball means that the adhesive layer patch has high resistance, in other words, it can adhere to the surface well. Adhesion ensures that the patch is not easily peeled off during use.

The XRD spectra of the patches before and after storage for 6 days are shown in Figure 4 and Figure 5, respectively. These XRD spectra are to observe the degree of crystallinity of sodium diclofenac in the patches compared to the spectrum of pure sodium diclofenac powder. In Figure 2, it can be seen that the spectra of sodium diclofenac in all samples (F1-F4) show lower peak heights and are similar to the spectrum of the patch blank.

This indicates a decrease in the degree of crystallinity of diclofenac sodium when formulated in patches either using cosolvents or not. To observe whether or not recrystallization of diclofenac sodium appears in the patch, storage is carried out for six days with the assumption that during storage, recrystallization of diclofenac sodium will occur. XRD spectra of diclofenac sodium in patches after 6 days of storage revealed that formulations without cosolvents, F3 and F4, showed an increase in peak intensity of the spectrum at several angles of reading the spectrum, while in F1 and F2 the spectrum was still similar to the initial spectrum. The increase in peak intensity in the XRD spectra of F3 and F4 indicates an increase in the degree of crystallinity of diclofenac sodium compared to the initial spectrum. This leads to the recrystallization of diclofenac sodium in the patch during storage.

Based on this observation, it can be said that the lipid-based cosolvent in this study was able to prevent recrystallization of the active substance in the patch. This can be explained that the cosolvent is able to increase the solubility of diclofenac sodium in the patch matrix so as to prevent matrix supersaturation conditions. The lipid-based cosolvent in this study also contains surfactants that can help the interaction of the drug in the patch so that it can keep the drug molecularly dispersed in the patch matrix. Cosolvent is able to inhibit the occurrence of supersaturation and reduce the risk of crystal growth by the mechanism of reducing surface tension by surfactants[27]. In conclusion, the addition of lipid-based cosolvents to the topical patch formulation of highly loaded sodium

diclofenac is able to inhibit crystallization after storage at room temperature for six days.

CONCLUSION

Addition of lipid-based cosolvents to the highly loaded sodium diclofenac topical patch formulation was able to prevent crystallization after storage at room temperature for six days.

Acknowledgments

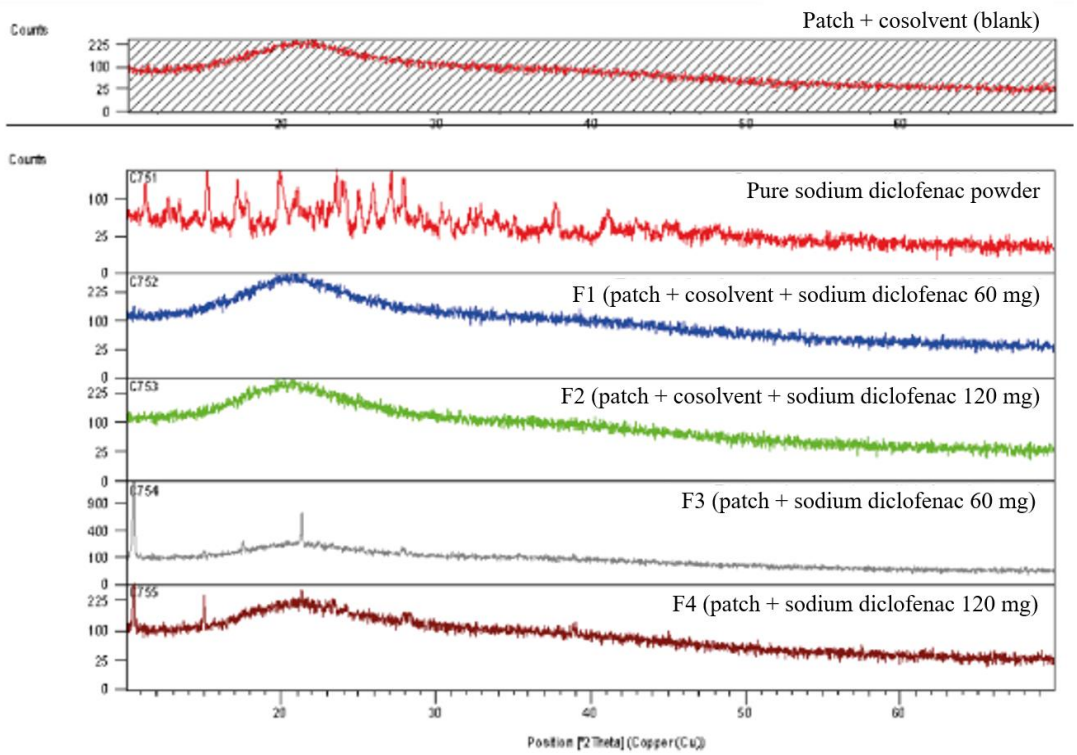

Figure 4: XRD spectra of fresh prepared patches containing cosolvent and diclofenac sodium compared to blank patches and patches with diclofenac sodium without cosolvent

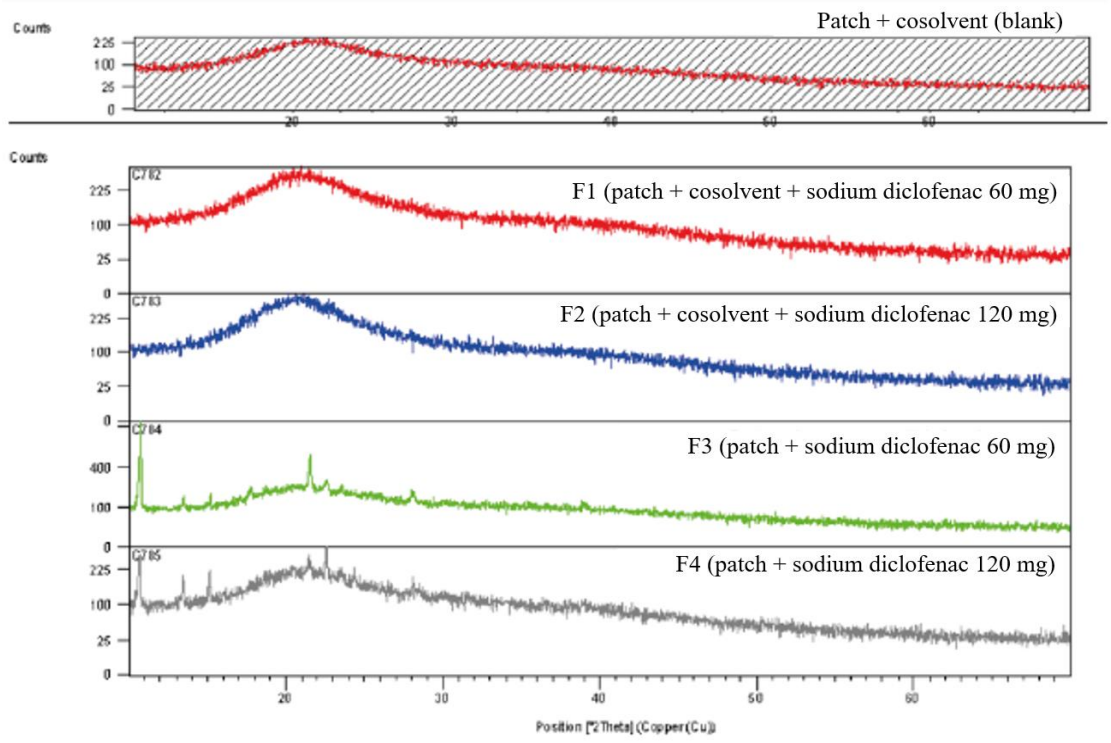

Figure 5: XRD spectra after storage for 6 days at room temperature of patches containing cosolvent and diclofenac sodium compared to blank patches and patches with diclofenac sodium without cosolvent

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