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# *FORMULATION AND CHARACTERIZATION OF ORGANIC- INORGANIC HYBRID FILM FOR TRANSDERMAL DRUG DELIVERY*

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**ABSTRACT**

A novel organic–inorganic hybrid film-forming gel for transdermal application was developed by poly vinyl alcohol using Di methyl polysiloxane as an inorganic-modifying agent, poly N-vinyl pyrrolidone as a tackifier and PEG 200 as a plasticizer. The hybrid film-forming gel can be directly applied on the skin forms a thin bioadhesive film with transparent and non- greasy feeling. The mechanical and bioadhesive properties of films produced from the hybrid gels were investigated and the results showed that the incorporation of appropriate Di methyl polysiloxane into the PVA matrix significantly improves the mechanical strength and skin adhesion properties of the resulting film. In conclusion, the bioadhesive films formed from organic–inorganic hybrid gel holds excellent qualities for application on the skin and may provide a promising formulation for transdermal delivery of drugs, especially when the patient acceptability from an aesthetic perspective of the dosage form is a main consideration.

## INTRODUCTION

Transdermal drug delivery system (TDDS) can provide some attractive performances over conventional pharmaceutical dosage formulations, such as avoiding hepatic first-pass metabolism, improving drug bioavailability, reducing dose frequency and stabilizing drug delivery profiles[1]**.** Compared with conventional system such as, transdermal patches, ointments and creams, the novel bioadhesive films are beneficial in term of ease of preparation, application, reduce skin irritation, less greasy, better skin adhesion properties, enhance the drug release and increase the patient acceptability from an aesthetic perspective[2]. Several types of polymeric materials have been studied over the last decade, in order to form bioadhesive films for controlled release of drugs through the skin[3]**.** These devices can improve the bioavailability of drugs that have presystemic hepatic metabolism and consequently optimize the pharmacotherapy thus Bioadhesive films can be applied to a variety of drugs, are of low cost and easy to apply, and allow immediate discontinuation of treatment for some side effect[4]. The attention of many researches has turned to the studies of the systems based on organic-inorganic hybrid substances. A growing interest is attributed to the diverse properties of such systems[5]. Organic-Inorganic hybrid materials are considered as next generation membrane materials having both film forming properties of a polymer and physicochemical stability of an inorganic compound. When applied to the polymer surfaces these combined materials show improved physical properties without neither cracks which are frequently found in inorganic materials nor poor thermal stability nor mechanical strength which always shadows organic materials[6]. Due to their numerous favorable characteristics, specifically the excellent film-forming properties, processability, biocompatibility, non-toxicity, remarkable hydrophilicity and chemical resistance films derived from poly vinyl alcohol (PVA) film-forming gels recently have attracted great attention and have been most widely used for transdermal delivery[7, 8]. Meloxicam (MLX) is a non-steroidal anti-inflammatory drug used orally to relieve the symptoms of osteoarthritis and rheumatoid arthritis has numbers of gastrointestinal side effects at high doses on long term treatment[9]. Like other NSAIDs, meloxicam is practically insoluble in water which leads to poor dissolution and, hence,

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variations in its bioavailability[10]. Therefore, meloxicam needs delivery system which modulates gastric side effect and delivers the drug to the inflammatory site. Hence present study includes the formation of gel based film for transdermal application of drug that will reduce the systemic side effects in addition will deliver the drug to the inflammatory site. Formation of film will provide better prolong adherence to the skin. In the present work, an organic–inorganic hybrid film-forming gel was developed for TDDS using PVA as the matrix, Di methyl polysilioxane (PDMS) as the modifying agent, poly(N-vinyl pyrrolidone) (PVP) as the tackifier and PEG as the plasticizer. The hybrid film-forming gel applied on the skin forms a thin and bioadhesive film having pleasing, transparent appearance without any greasy feeling.

## MATERIAL AND METHODS

### Materials

Meloxicam was obtained as gift sample from Lupin Pharmaceuticals Ltd., Goa, India. Dimethyl polysiloxane and D, L Lactic acids were procured from Hi media Laboratories Pvt ltd, Mumbai, India. Polyvinyl alcohol, Dimethyl sulfoxaide and Poly ethylene Glycol 200/400 purchased from Qualigens fine chemicals, Mumbai, India. All other chemicals were of the analytical grade and used as received.

### Methods

#### Preparation of organic–inorganic hybrid film-forming gel

The organic–inorganic hybrid gel was prepared by sol gel process[11]. 5% polyvinyl alcohol solution was prepared in hot distilled water, to this specified amount of Dimethyl polysiloxane (PDMS) and 2 mL of D, L-lactic acid was added to initiate the cross-linking reaction. The mixed solution was gently stirred for 12 h at room temperature. Additionally, the solution of Meloxicam in DMSO was prepared. Subsequently, 0.5 g PVP and PEG 200 with or without drug solution were added into the aforementioned solution. Again, the mixture was stirred slowly for 4 h at room temperature and left overnight to remove the entrapped air. The final gel was stored in glass vials sealed tightly with an aluminum cap. To study the effect on bioadhesion and drug release of various ratios of PVA and PDMS were selected. All the formulations F1 to F12 contain 15 mg meloxicam per grams. The composition of batches F1 to F12 are as shown in table 1.

**Table 1: Composition of Meloxicam Hybrid Gel**

| Formulation Code | PVA : PDMS | PVP K30 (g) | PEG 200 (g) |
|---|---|---|---|
| **F 1** | 9 : 1 | 0.5 | 1.8 |
| **F 2** | 8 : 2 | 0.5 | 1.6 |
| **F 3** | 7 : 3 | 0.5 | 1.4 |
| **F 4** | 6 : 4 | 0.5 | 1.2 |
| **F 5** | 5 : 5 | 0.5 | 1.0 |
| **F 6** | 10 : 3 | 0.5 | 0.3 |
| **F 7** | 10 : 4 | 0.5 | 0.3 |
| **F 8** | 10 : 5 | 0.5 | 0.3 |
| **F 9** | 10 : 6 | 0.5 | 0.3 |
| **F 10** | 10 : 7 | 0.5 | 0.3 |
| **F 11** | 10:0 | - | - |
| **F 12** | 10:0 | 0.5 | 0.3 |

### Evaluation of Film Forming Hybrid Gel:

#### Bioadhesive and mechanical properties of organic–inorganic hybrid gel

#### Measurement of pH

The pH of various gel formulations was determined using digital pH meter. One gram of gel was dissolved in 100 ml distilled water and stored for two hours. A mean value of three readings was taken.

#### Viscosity measurements

A viscometer (Brookfield DV-II) was used to measure the viscosities of the hybrid gels. The spindle was rotated at 10 rpm. Samples of the gel were allowed to settle for 30 min before the measurements were taken. A mean value of three specimens was taken[12].

#### Determination of bioadhesive force

The bioadhesion force is an important parameter for film forming formulations since it increases its residence time on the skin. The bioadhesive force of hybrid gel was determined by using modified method described by[13]. A section of abdomen mucosal tissue of rat placed onto each glass vial using a rubber band and an aluminum cap. The vials with the tissues were placed in beaker containing phosphate buffer pH 7.4 maintained at 36.5°C for 10 min. Next, one vial with a section of tissue was connected to the balance and the other vial was placed on a height-adjustable pan. Hybrid gel was added onto

the abdominal tissue on the other vial. Then, the height of the vial was adjusted so that the hybrid gel could be placed between the abdominal tissues of both vials. The weights kept increase until two vials were attached. Bioadhesive force, the detachment stress (gm/sq.cm), was determined from the minimal weights that detached two vials. The stronger the bioadhesive force, the more it can adhere to the skin surface.

**Drug content studies**

Drug content of the gel was determined by dissolving 100 mg of gel in about 10 ml of phosphate buffer pH 7.4. From this 1.0 mL solution was diluted up to 10.0 mL and finally the absorbance of prepared solution was measured at 365 nm by using UV visible spectrophotometer.

**Spreadability[14]**

For the determination of spreadability, excess of sample was applied between the two glass slides and was compressed to uniform thickness by placing 1000 g weight for 5 min. Weight (50 g) was added to the pan. The time required separating the two slides, i.e. the time in which the upper glass slide moves over the lower plate was taken as measure of spreadability (S)

$$S=\frac{M\times L}{T}$$

Where,M is weight tide to upper slide, L is length moved on the glass slide and T is time taken.

**Preparation of Bioadhesive Organic Inorganic Film**

The accurately weighed quantity of film-forming gel was coated on a Teflon plate in a rectangular mould in a dust-free atmosphere at room temperature. The film was allowed to dry at 40°C for about 72 h, and the completely dried film was subsequently peeled off and stored meticulously for the further study.

**CHARACTERIZATION OF HYBRID FILM**

**Mechanical Properties of the film[12]**

In order to evaluate the mechanical properties, completely dried film of various formulations of film-forming gels were obtain. The film was cut into strips of 1 × 3 $cm^2$ size. Each strip was measured by a Vernier Caliper for thickness at five different points along the length. Mechanical tests including break stress and strain of all samples were performed at room temperature using universal testing machine, with load cell range 0-40 N. Films of dimension 5 x 1.5 $cm^2$ and free from physical imperfections were used for the study. The films were held between two clamps at distance of 5 cm. The hybrid films were pulled by the clamp at the rate 50 mm/min. The mechanical properties tensile breaking stress and % elongation were calculated for the film from the above measurements.

**Water vapour permeability (WVP) of film**

The water vapor permeability (WVP) was investigated according to the method specified in British Pharmacopoeia with slight modification. Circular samples with a diameter of 2.0 cm were cut from the dry film sheets with a scalpel. Twenty-milliliter glass vials with an opening of 1.5 cm diameter were filled with approximately 10 g of distilled water, and the vials were weighed before sealing. The vials covered with the circular film samples were sealed tightly and placed into a test chamber. The inside environment of the test chamber was kept at 37°C and a relative humidity of 65%. They were kept for 24 h and weighed at predetermined intervals after removal from the test chamber. The control for this experiment was vial without film sample which represented 100% water vapor permeability.

***In vitro* release study**

The release of drug through diffusion membrane as the diffusion barrier was examined using a modified Franz-type diffusion cell. Diffusion membrane with a diameter of 1.5 cm was mounted on the diffusion barrier in the donor compartment. After acclimation for 1 h, the receptor compartment was filled with phosphate buffer pH 7.4. The solution in the receptor compartment was thermoregulated with a water bath at 37 ± 0.5°C and stirred with a small magnetic bar. Samples (2 mL) were withdrawn at 1, 2, 3, 4, up to 12 hours. Subsequently, the receptor compartment was replenished to its marked volume with fresh buffer solution. Addition of solution to the receptor compartment was performed with great care to avoid trapping air beneath the membrane samples

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**Appearance of Film on Skin**

The appearance of film-forming gel was observed by applying gel on the inner surface of the forearm of volunteers at room temperature and the changes occurring in the appearance of the film was noted.

## RESULT AND DISCUSSION

### Bioadhesive and mechanical properties of organic–inorganic hybrid gel

The gel of all the batches was evaluated for their pH. From table 2 it was found the pH of all the formulations from F1 to F12 ranges from 5.9 to 7.2 that come in the range of normal skin pH. Bioadhesive is an essential property of film for a transdermal therapeutic product[11]. The bio adhesion of PVA–PDMS–PVP–PEG films found to be markedly increased with the increase in the amount of PDMS as illustrated in table 2 probably as a result of cross-linking of PDMS can increase intermolecular force and strengthen the hydrogen bond action due to increasing amount of Si-O- in the system. Additionally these factors can lead to increase in viscosity as depicted in table 2. One of the most important parameter is the content of active ingredient in the formulations. From the table 2 it was found that the drug content of all the formulations F1 to F12 was more than 89.2 % (average drug content 94.67±1.024%). All the formulations from F1 to F12 had the spreadability ranging from 19.59 to 25.59 (average spreadability 23.41 (gm.cm/sec)).

### Mechanical properties of organic–inorganic hybrid films

The topical application of polymeric films depends on their mechanical properties at room temperature. The stress–strain readings for PVA and its hybrid films with different PDMS content are shown in table 3. It can be seen that neat PVA film (F11) was very brittle with high level of mechanical stresses due to strong crystallization. PDMS had a significant impact on mechanical properties of the hybrid films. Compared with PVA–PVP–PEG (F12), the stress of the hybrid films was markedly improved with increasing PDMS content and the degree of elongation decreased with the increase in PDMS, which can be attributed to the strong interaction between PVA and silica. So, the addition of PDMS into the bulk of PVA matrix was rational to improve toughness of the hybrid films in order to ensure excellent application performance.

The thickness (mm) of all the films of size 1 × 3 $cm^2$ along the length was found to be 0.0724 ± 0.021mm. It was known that the occlusion of skin not only resulted in hydration but also alter other ecological factors and often cause severe skin irritation[15]. Therefore, WVP of films was an important feature of a drug delivery system that was supposed to be on the skin for a prolonged period of time. The WVP of PVA and its hybrid films was assessed according to British Pharmacopoeia. The WVP of control value and PVA film was about 0.185 g ($cm^2$ 24 $h)^{-1}$ and 0.062 g ($cm^2$ 24 $h)^{-1}$, respectively. The relatively low WVP value of PVA film indicates large number of crystalline regions that are impermeable to water vapour diffusion. It can be observed from figure 1 and figure 2 that the content of PDMS had a considerable effect on the WVP of PVA films. But, a parabolic relationship was observed between the WVP of PVA films and the PDMS content. The WVP values firstly increased with the increase in the PDMS/ (PVA + PDMS) ratio (from F1to F3) and then rapidly decreased with a further increase in the content of PDMS. PDMS can effectively disorder the PVA chains and hence decrease the crystalline region of PVA, which made water vapour diffusion easier. The self-cross-linked reaction of PDMS molecules proceeded at higher PDMS content (PDMS/ (PVA + PDMS) and thereby, the destruction of crystalline regions of PVA was depressed due to the decrease in cross-link reaction between PVA and PDMS

### Characterization of Film

#### *In vitro* Release study

The results of release of meloxicam from PVA and its hybrid films across dialysis membrane are shown in figure 3, 4, and 5. The formulation F1 to F5 (Figure 3) show the 8.94 ± 0.41, 11.52 ± 0.94, 24.67 ± 0.78, 23.88 ± 0.93, 7.75 ± 0.67 % release at 1hr while it shows the 77.37 ± 2.24, 83.79 ± 1.23, 92.18 ± 1.06, 95.2 ± 2.18, 74.45 ± 0.93 % release at 10 hr. From the above formulations F4 containing 40% PDMS showed maximum release i.e. 95.2 ± 2.18. The above result shows that the formulation containing PDMS in the ratio of 20% to 40% shows the maximum drug release. Batch F6 to F10 (Figure 4) showed 8.71 ± 1.42, 22.09 ± 0.86, 23.51 ± 1.68, 5.02 ± 1.47, 3.15 ± 0.40 % release at 1hour while these batches shows 79.79 ± 0.90, 95.06 ± 1.30, 93.33 ± 0.78, 74.83 ± 2.50, 57.52 ± 0.65 % release at 10 hr.

The above result shows that the formulation containing 10:3 and 10:4 (PVA: PDMS) i.e. batch F7 and F8 shows maximum drug release. F11 (PVA) and F12 (PVA–PVP–PEG) as shown in figure 5, showed more sustained release of drug i.e. 70.34 ± 1.01 and 74.20 ± 2.17 after 10 hr which is less than the formulation containing PDMS. Such effect may be due the

diffusion process of drug within the film become very difficult due to the crystallization of PVA chain. However, the % release of meloxicam from PVA–PVP–PEG film was found to be slightly higher than that from PVA film, which can concluded that addition of PVP and PEG enhanced the diffusion of drug, as the crystallization of drug in the matrix may cause a reduction in drug diffusion[16]. From the results discussed above batch F4 shows better results for bioadhesion study along with the percent drug release study. The PVP in film can improve the drug diffusion because the anti-nucleating effect of PVP can convert the crystalline drug into the amorphous state. In addition, PEG may create a space and a large free volume within the film, therefore enhancing drug diffusion. As observed from figure 3, 4and 5 introduction of PDMS can exert a strong impact on the drug diffusion through the hybrid films. Especially, the % release of drug was increased when the PDMS/ (PVA + PDMS) ratio is between 20% and 40% and then rapidly decreased with a further increasing PDMS. The studies above have clearly shown that the appropriate amount of PDMS can effectively increase the amorphous region of the matrix and accordingly enhance drug diffusion. On the other side, the excessive PDMS leading to self-crosslinked reaction of PDMS made the film more compact and thereby made drug diffusion more difficult.

**Table 2: Evaluation of Film Forming Hybrid Gel**

| Formulation Code | pH | Viscosity (cps) | Bioadhesive force (g/sq.cm) | % Drug content | Spreadability (gm.cm/sec) |
|---|---|---|---|---|---|
| **F 1** | 6.79 ± 0.09 | 30440 | 2.029 ± 0.06 | 92.84 ± 1.04 | 22.94 ± 0.73 |
| **F 2** | 6.95 ± 0.14 | 31620 | 2.494 ± 0.017 | 89.28 ± 1.83 | 24.57 ± 1.08 |
| **F 3** | 6.89 ± 0.23 | 34740 | 2.682 ± 0.06 | 96.71 ± 1.24 | 25.59 ± 0.47 |
| **F 4** | 6.88 ± 0.06 | 35900 | 3.031 ± 0.041 | 97.23 ± 0.68 | 23.37 ± 0.54 |
| **F 5** | 7.23 ± 0.03 | 36680 | 3.152 ± 0.022 | 89.65 ± 0.53 | 24.90 ± 0.73 |
| **F 6** | 6.84 ± 0.25 | 30435 | 2.587 ± 0.012 | 94.65 ± 1.05 | 21.99 ± 0.51 |
| **F 7** | 6.70 ± 0.21 | 31920 | 2.705 ± 0.026 | 97.84 ± 0.34 | 22.40 ± 0.53 |
| **F 8** | 6.91 ± 0.02 | 33480 | 2.983 ± 0.033 | 96.38 ± 1.13 | 23.20 ± 1.10 |
| **F 9** | 7.06 ± 0.05 | 35120 | 3.000 ± 0.08 | 96.29 ± 1.35 | 24.45 ± 0.87 |
| **F 10** | 6.92 ± 0.12 | 37640 | 3.211 ± 0.019 | 95.92 ± 1.05 | 25.68 ± 0.90 |
| **F 11** | 5.95 ± 0.5 | 28540 | 1.425 ± 0.08 | 91.33 ± 2.04 | 19.59 ± 0.65 |
| **F 12** | 6.18 ± 0.28 | 28680 | 1.544 ± 0.05 | 92.55 ± 1.02 | 22.31 ± 0.83 |

**Table 3. Mechanical properties of organic–inorganic hybrid films**

| Formulation Code | Breaking Stress ($gm/cm^2$) | % Elongation | Thickness (mm) | Water permeability test $gm\ (cm^2 24h)^{-1}$ |
|---|---|---|---|---|
| **F 1** | 3.312 | 86 | 0.0724 ± 0.02 | 0.070 |
| **F 2** | 3.64 | 74 | 0.0719 ± 0.02 | 0.094 |
| **F 3** | 4.14 | 76 | 0.0723 ± 0.01 | 0.105 |
| **F 4** | 4.74 | 48 | 0.0714 ± 0.02 | 0.083 |
| **F 5** | 5.32 | 28 | 0.0720 ± 0.02 | 0.073 |
| **F 6** | 2.59 | 68 | 0.0734 ± 0.01 | 0.100 |
| **F 7** | 3.65 | 51 | 0.0718 ± 0.02 | 0.110 |
| **F 8** | 4.92 | 51 | 0.0724 ± 0.03 | 0.122 |
| **F 9** | 5.445 | 38 | 0.0724 ± 0.02 | 0.098 |
| **F 10** | 6.19 | 29 | 0.0722 ± 0.02 | 0.091 |
| **F 11** | 5.71 | 15 | 0.0723 ± 0.01 | 0.062 |
| **F 12** | 3.04 | 92 | 0.0724 ± 0.02 | 0.185 |

**APPEARANCE OF FILM ON SKIN**

Film-forming gel was applied on the inner surface of the forearm of volunteer at room temperature. Figure 6 shows the appearance of film after 2 hrs of application. The organic–inorganic hybrid film-forming gel was transparent, jelly-like substance with good flexibility and adhesive property, easy to apply on the skin surface. The viscous gel turned entirely into a solid film and adhered tightly with skin after acclimation for about 10 min. The resultant film can form a smooth hard outer surface which may reduce the risk of polluting clothes or being rubbed off by clothes. The film was maintained and satisfactorily adhered on skin. Film formed on skin was quite different from traditional ointments and creams. In addition without any greasy feeling, the film formed from organic–inorganic materials not only can maintain suitable skin adhesive properties to ensure long time dressing, but also have enough strength to resist abrasion. This result indicated that PDMS can exert a significant influence on the physicochemical properties and application performances of the resultant film.

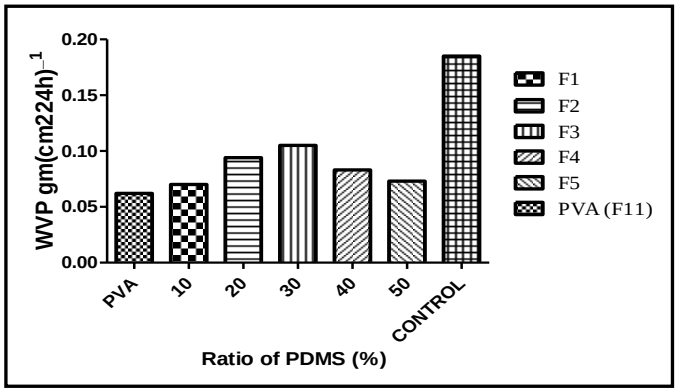


**Figure 1:** WVP of PVA and Hybrid Films F1- F5

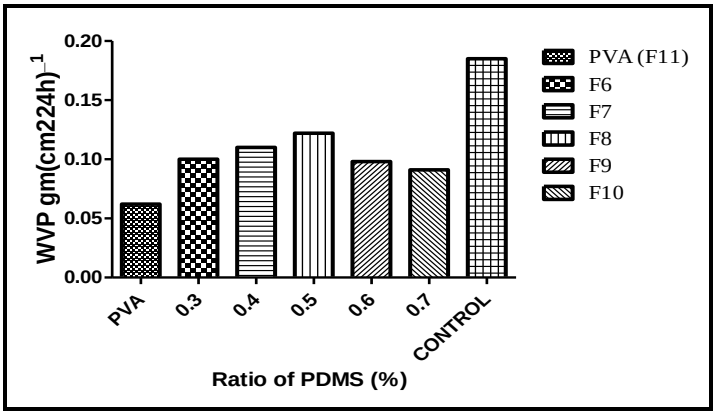


**Figure 2:** WVP of PVA and Hybrid Films Form F6 - F10

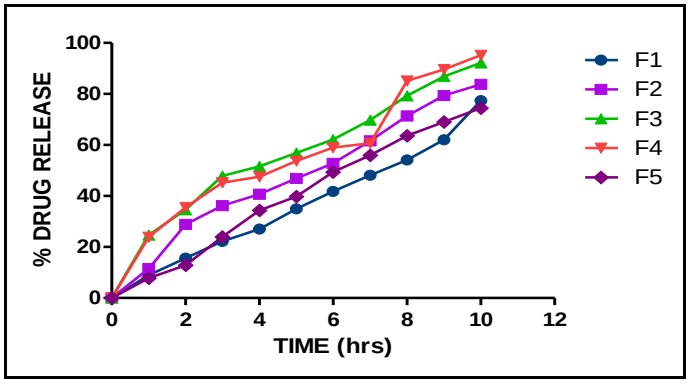


**Figure 3:** Percentage drug release of batch F1-F5

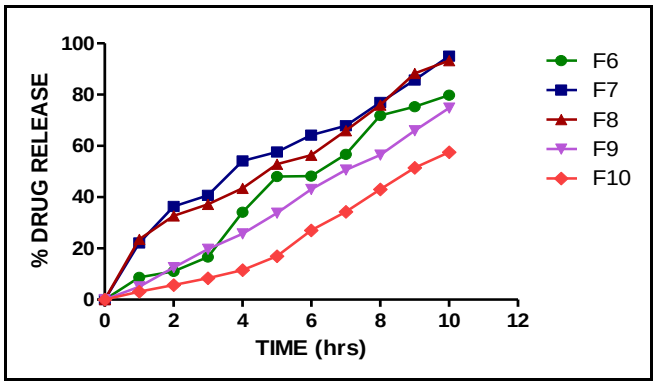


**Figure 4:** Percentage drug release of batch F6-F10

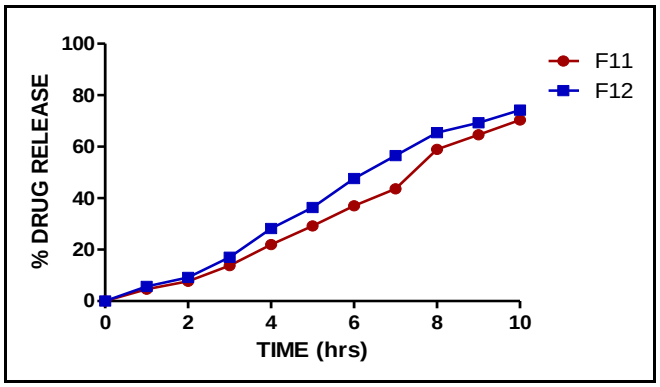


**Figure 5:** Percentage drug release of batch F11-F12

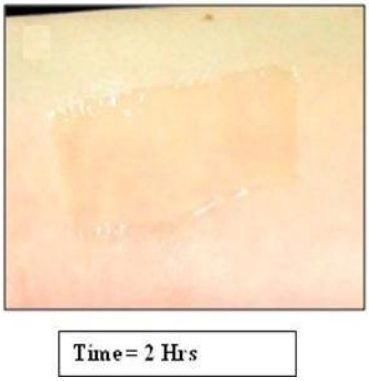


**Figure 6:** Appearance photographs of Hybrid films after 2 hrs

## CONCLUSIONS

A novel organic–inorganic hybrid film forming gel composed of PVA, Di methyl polysilioxane, PVP and PEG 200 was used to prepare transdermal film. Film formed on skin was quite different from traditional ointments and creams. Apart from without any greasy feeling, the film formed from organic–inorganic materials not only can maintain suitable skin adhesive properties to ensure long time dressing, but also have enough strength to resist abrasion. This film-forming gel was colorless, transparent with good flexibility and adhesion property with an aesthetical appearance. This result indicated that PDMS can exert a significant influence on the physicochemical properties and application performances of the resultant film. In nutshell, the novel formulation of hybrid gel may provide a realistic explanation to the aforementioned problems associated with the use of polymer gel as a film forming agent for TDDS.

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