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Research Article

Influence of Critical Manufacturing Parameters on Drug Release of Fentanyl Reservoir Transdermal Patches

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ABSTRACT

The objective of this study was to determination of critical manufacturing parameters (CMP) and their influences on drug release of fentanyl transdermal reservoir patches (RPs). Fentanyl as a common drug administered by RPs was used as a model for drug release testing. Drug release studies were carried out using paddle over disk (USP apparatus 5). The critical manufacturing parameters (CMP) may potentially influence on rheological properties of hydroxyethyl cellulose (HEC) gels include gelation temperature and hydration time of polymer. Rheological characterizations were examined using a spindle type rheometer with a thermostatic water pump bath. The results indicated that the viscosity and consistency of 3% gel made in 60 °C was suitable for fentanyl RPs and showed desired drug release over 72 h. While the release of fentanyl from gel made in 40 °C reached its maximum within 48 h. Increasing the HEC concentration or in gelation temperature, both significantly decreased the release rate of fentanyl. In contrast, the hydration time of polymer did not affect significantly on drug release. Flow curve of HEC gels showed non-Newtonian characteristics, pseudo-plasticity for 2% gel and Bingham behavior for 3% or more. Gels with 3% concentrations showed some thixotropy. The thixotropic coefficient (M) and yield value (f) were 417 mPa s and 820 dynes cm^{-2}.

INTRODUCTION

Delivering of drugs into systemic circulation through skin has generated a large number of interests during the last couple of decades [1]. Fentanyl with an analgesic potency of about 80 times that of morphine and lipophilic characteristics make it a good candidate for transdermal drug delivery system (TDDS) [2].

The key parameter for any TDDS is its efficacy as demonstrated in controlled clinical trials. The time and expense associated with such trials make them unsuitable as routine quality control methods. Therefore, *in vitro* surrogate tests are often used to assure that product quality and performance are maintained over time and in the presence of change [3]. More recently, *in vitro* release testing has shown promise as a means to comprehensively assure consistent delivery of the active component(s) from transdermal products [4].

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An *in vitro* release rate can reflect the combined effect of several physical and chemical parameters, including solubility, particle size of the active ingredient and rheological properties of the dosage form [5].

In general, TDDSs are complex formulations having different structural elements which several critical manufacturing parameters (CMP) can influence on their characteristics. Variations in the manufacturing procedure of transdermal patches are likely to be critical to their drug release profiles [3, 6]. The most important CMP in manufacturing of fentanyl patches which investigated in this paper were gelation temperature and hydration time of HEC. The CMP affects on various factors, including the product rheology and viscosity. These factors combine to determine the release characteristics of the fentanyl from patches.

Rheological investigations are used as important tools in pharmaceutical development and quality control of dosage forms [7]. The rheological behaviors of gels, polymers and pressure sensitive adhesives are an important key factor

in manufacturing of different TDDS including reservoir patches (RPs) and matrix patches (MPs) [8]. For example the consistency of polymer solution in MPs should be enough causes no running beneath the lab film coater, on the other hand, high viscosity leads to defect and incomplete film layer on backing layer. On the other hand, the viscosity of a given polymer with known concentration depends to method of preparation, hydration time and the gelation temperature [9]. According to Stokes-Einstein equation there is a reciprocal relationship between diffusion coefficient (D) and viscosity (η). Therefore, changing in viscosity that may be happened by deliberately or accidentally changing in manufacturing process lead to varying in D value [10].

$$D = \frac{RT}{6\pi\eta r}$$

In which R is gas constant, T is absolute temperature, η is viscosity and r is radius of molecule [10].

EXPERIMENTAL

MATERIALS

Micronized fentanyl was obtained from Diosynth (the Netherlands). Hydroxyethyl cellulose (HEC, Natrosol® 250 G grade) was from Hercules (Aqualon division, Germany). All backing, control membranes and liners were donated by 3M (USA). Support membrane (Spectra/por® 7 with cut off 14000 Daltons) to fix patches in dissolution vessel was purchased from Spectrum (USA). All solvents and reagents used were analytical reagent grade and solutions were prepared with purified water (conductivity less than 1μS cm^{-1}).

METHODS

Preparation of HEC Gel for RPs

Accurately weight of fentanyl was dissolved in specified volume of ethanol. The polymer powder, HEC (2, 3 and 4 % w/w), was added and hydrated slowly in specified quantity of water at room temperature within 1 h or 24 h with a magnetic stirrer (IKA, Germany). Excessive foam and lump formation was to be avoided. After aforementioned hydration periods, HEC was gelled in 40°C or 60°C. Finally fentanyl solution was added to polymer gel. The following mandatory instructions should be taken into consideration when dispersing HEC to obtain reproducible rheological properties: the diameter of the magnetic bar should be approximately one third of the diameter of the beaker, the revolution speed of the bar should be sufficient to keep the whole of the contents in motion, the stirrer should create a vortex which causes from the very outside of the surface, the HEC powder should be sprinkled slowly onto the region of the vortex in a steady stream to avoiding undue accumulation and lump of polymer on the liquid surface.

The RPs were made by applying an appropriate amount of HEC gel containing fentanyl and sealing their rims at 150 C for 4-8 seconds by a heat sealing device developed in our laboratory [11].

Rheological Studies

Evaluation of Rheological Behaviors of HEC Gels

The rheograms of the gels were obtained at 25 ± 0.1 °C using a rotating spindle type and programmable rheometer (Brookfield DV III, USA) and thermostatic water pump bath (Brookfield TC-101, USA). Rheocalc® software was used to control of rheometer as well as acquisition and processing the data.

To obtain uniform and reproducible rheological results, measuring HEC viscosity was carried out according to following instruction: while the temperature of gel was maintained at 25 ± 0.1°C, corresponding to the viscosity and concentration of HEC the appropriate Brookfield viscometer spindle No. 2 or 3 selected and inserted into the gel. At each speed, the rotating of spindle was kept for 3 minutes before taking the reading. The torque percent of rheometer for each reading was between 10 to 90% and readings out of this range were excluded. The viscosity of gel was determined between 30 and 60 minutes after removal from stirrer. If gel stands longer than 60 minutes, it was returned to stirrer for 10 minutes and placed in bath for 30 minutes and then its rheogram was determined.

Three aforementioned concentrations of HEC were prepared and their rheological behaviors compared regarding two parameters, hydration time and gelation temperature. In the first study, the wetting of polymer performed within 1 h and 24 h and in the second study the gels were prepared in 40°C and 60°C. The shearing rates (SR) and corresponding shearing stresses (SS) were measured and flow curves or rheograms obtained by plotting SS versus SR [12, 13].

Measurement of Thixotropic Coefficient by Increasing Shear Rate

A flow test was used to determine the structural breakdown due to increasing shear rate. For the up-curve, a controlled and continuous ramp of shear rate was applied at 25°C. The same procedure was used for the down-curve with reversed shear rate to measure thixotropy. The thixotropic coefficient (M), the loss in SS per unit increase in SR was obtained from following equation:

$$M = \frac{(U_1 - U_2)}{\ln(v_2 / v_1)}$$

In which U_1 and U_2 are the plastic viscosities for two separate down-curves having maximum SR of v_1 and v_2 [10, 12].

***In vitro* Release of Fentanyl**

Determination of fentanyl release pattern in transdermal patches was carried out using USP 27 apparatus 5, paddle over disk, with the speed of 50 rpm [13]. One patch was applied flat on the disk with the release surface facing up (effective area available to diffusion was 10 cm^2) and a spectra/por® 7 with cut off 14000 Daltons, as a support membrane, on top of it. This membrane was rehydrated by immersion in purified water for 1 h before application. At predetermined time intervals, 5mL samples were collected and immediately replenished with fresh medium [11, 14].

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 stationary phase was µ bondapack C18 (300 × 3.9 mm) column maintained at 40 °C. The mobile phase was 40:60 of ammonium acetate solution (1 in 100) and a mixture of methanol, acetonitril, and glacial acetic acid (400: 600: 0.6). The pH of mobile solution was adjusted at 6.6 ± 0.1 by drop-wise addition of glacial acetic acid [15].

RESULTS AND DISCUSION

Results of Rheological Studies

Rheological results of HEC. - The apparent viscosity of 2, 3, and 4 % w/v gels in low shearing rate are around 850, 4400 and 13200 cps, respectively. As it is shown in Fig. 1, there are significant differences in their rheograms even in low shearing rate. It seems by increasing the concentration of HEC, the gels show the plastic or Bingham behavior rather than pseudo-plastic characteristic. The yield value (f) of HEC 3% gel was measured by extrapolation of straight part of rheogram to SS axis [10, 12]. The f value for HEC 3% gel was 820 dynes cm^{-2}. It should be noted that plastic flow and some yield value is desirable in RPs due to desirable applying and no pouring of gel on the liner. So, it was concluded that the consistency of HEC 3% gel is suitable for RPs.

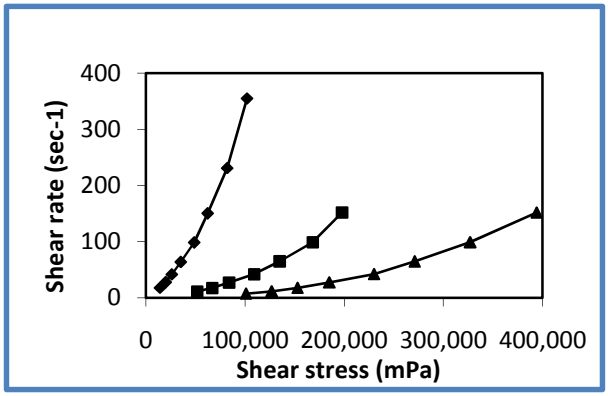

Figure 1: Comparing of rheological behaviors of three different concentrations of HEC gels: ♦ - HEC 2%, ■ - HEC 3%, and ▲ - HEC 4%.

After finding the appropriate concentration of HEC, the influence of hydration time of HEC before warming and gelling was studied. As shown in Fig. 2, the hydration time more than 1 h can cause no significant influence on viscosity, $p<0.05$. It means that on standby condition the viscosities of two gels are close to each other, for example in low shearing rate 11.6 sec^{-1}, the apparent viscosities of two gels are 4270 and 4080 cps, respectively.

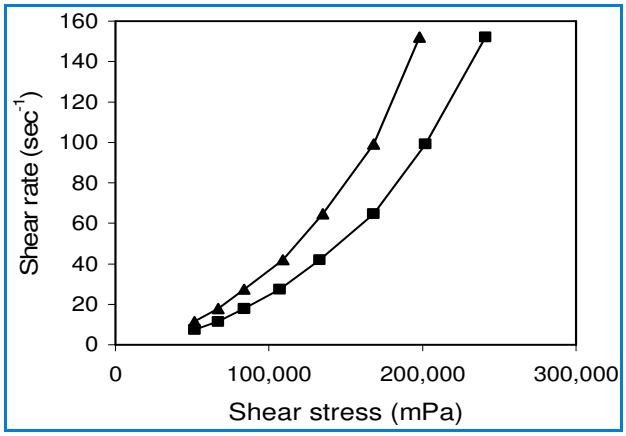

Figure 2: No significant influence ($p<0.05$) of hydration time on rheological behavior of HEC 3%. ▲ - HEC 3% with 1 h hydration time and ■ - HEC 3% with 24 h hydration time.

In the next study, as shown in Fig. 3 the significant influence of gelation temperature was found. The apparent viscosity of gels prepared in 40 °C and 60° C in low shearing rate 11.6 sec^{-1}, were 4080 cps and 8250 cps, respectively. So, it was concluded that the influence of gelation temperature is much more important than hydration time on viscosity especially in low shear rate, standby condition.

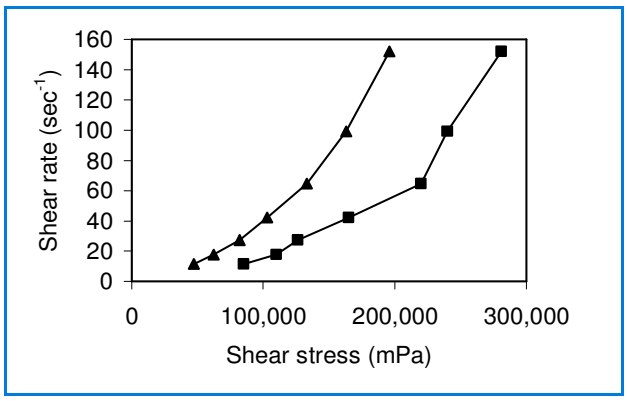

Figure 3: Significant influence ($p<0.05$) of gelation temperature on rheological behavior of HEC 3% gels. ▲- gelation in 40°C, ■ - gelation in 60° C

Thixotropic Results

The calculation of thixotropic coefficient (M) showed that its value was 417 mPa s. As shown in Fig. 4, in this approach to measure M value, two hystersis loops were obtained having different maximum SR, v_1 and v_2. The slopes of two down-curves are reciprocal of viscosities.

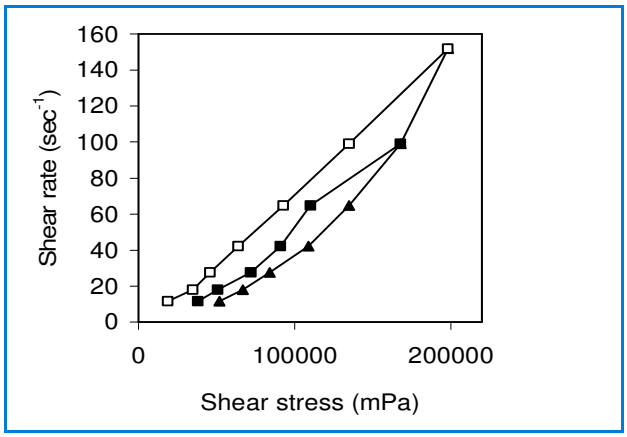

Figure 4: Structural breakdown of HEC 3% gel and its thixotropic property when subjected to increasing SR. ▲ – up-curve rheogram ■ - first down-curve rheogram, and □ - second down-curve rheogram.

Drug Release Results

The drug release from two RPs were made with HEC 3% gelled in 40 °C and 60 °C was compared using USP Type V apparatus. Drug release data are summarized in Table 1. The effects of changing in gelation temperature are shown in Fig. 5. Although the concentration of HEC is 3%, but there is a significant difference in their drug release. So, it is concluded that in the manufacturing RPs the CMP is gelation temperature. The time needed to release about 90% fentanyl from HEC 3% gel made in 40 °C and HEC 3% gel made in 60 °C were 48 and 72 h, respectively. It means CPM is important in manufacturing semi-solid gel and viscosity determines release profile.

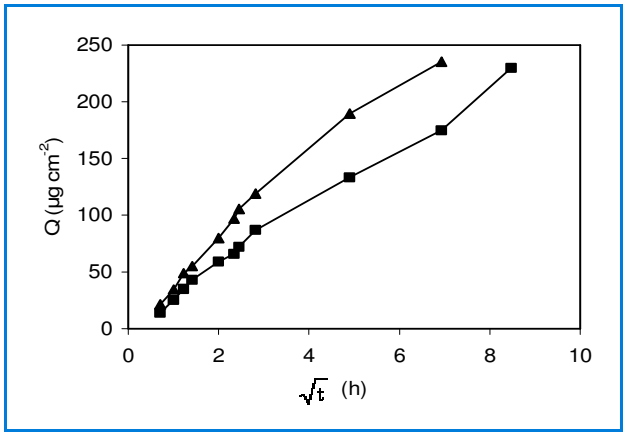

Figure 5: Drug release from fentanyl RPs made with HEC gelled in: ■ - 60 °C, and ▲- 40 °C.

Table 1: Drug release data for fentanyl RPs made with HEC gelled in 40 °C and 60 °C.

Time		HEC gelled in 60 °C		HEC gelled in 40 °C	
(h)	$\sqrt{t}$	Amount (µg)	Q (µg cm^{-2})	Amount (µg)	Q (µg cm^{-2})
0.5	0.71	140	14	213	21.3
1	1	252	25.2	345	34.5
1.5	1.22	350	35	489	48.9
2	1.41	431	43.1	552	55.2
4	2	590	59	800	80
5	2.34	660	66	970	97
6	2.45	720	72	1054	105.4
8	2.82	870	87	1190	119
24	4.9	1335	133.5	1897	189.7
48	6.93	1750	175	2354	235.4
72	8.48	2300	230	2380	238

CONCLUSION

In vitro experiments showed manufacturing procedures are critical in semi-solids used in RPs. Prominent effects of CPM on rheological properties and release of fentanyl from RPs were observed. Higher rate of drug release from the formulations made with HEC gelled in 40 °C as compared to 60 °C were showed. The results also established the tight dependence of drug release to viscosity of polymer. The results also indicate that due to hydrophobic nature of fentanyl, a major fraction of drug incorporated in the emulsion-gel is entrapped in the polymer network. Evidence also showed that concentration of HEC has a profound influence on the drug release. The hydration time need for dispersion of polymer more than 1 h cannot influence on viscosity of HEC. Finally, we suggest running a multi-points drug release test for any changing in manufacturing site, equipments and procedures before and after changing and comparing the rheological behaviors of semi-solid products to insure the reproducibility of results. Measuring the thixotropic coefficient and yield vale as two important rheological properties is a proper way to produce batch to batch uniformity.

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