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Formulation and evaluation of 4-benzylpiperidine drug-in-adhesive matrix type transdermal patch

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ABSTRACT

The objective of our study was to develop a transdermal patch of 4-benzylpiperidine and to evaluate its *in vitro* transdermal permeation profile. Appropriate pressure sensitive adhesives and additives were selected based on solubility and slide crystallization studies. Release liners and backing membranes were selected based on their ability to peel without leaving a residue and their affinity to formulation respectively. Drug-in-adhesive patches developed were investigate for their *in vitro* drug permeation over 48 h across dermatomed human skin using Franz diffusion cells. Silicone based pressure sensitive adhesive along with colloidal silicon dioxide as viscosity builder, fluoropolymer coated membranes as the release liner and polyester based membranes as backing were chosen to develop a drug in silicone adhesive patch. Polyisobutylene adhesive based patch was developed with drug in polyisobutylene adhesive, along with oleic acid and oleyl alcohol as permeation enhancers, polyester for the release liner and polyethylene as backing. Among the patches developed, polyisobutylene adhesive based patch with higher drug concentration exhibited superior transdermal permeation (1608.5 ± 53.4 μg/cm^2 over 48 h). The final patch was further tested for uniformity in coat weight, shear strength, tack and peel adhesion.

1. Introduction

Cocaine remains one of the most used illicit drugs worldwide with an estimated 17 million users in 2015, making it a major public health issue (United Nations publication, 2017). Despite its negative health consequences and addictive potential, there is no FDA-approved pharmacotherapies (Vocci et al., 2005; Vocci and Appel, 2007; Volkow and Li, 2004). Another such major public health issue with an estimated worldwide occurrence of about 5% in children (Polanczyk et al., 2014), and symptoms that continue into adulthood in up to 65% of patients (Faraone et al., 2006), is attention-deficit/hyperactivity disorder (ADHD). The incidence of adult ADHD appears to be much higher in individuals with cocaine-use disorder, compared to the general population. In a sample of adult patients seeking treatment for cocaine addiction, 35% were found to have ADHD. These numbers are in line with the assumption that adolescents with ADHD are about twice as likely as healthy individuals to develop a substance use disorder due to the impact of neurotransmitter systems in the brain thought to be altered in ADHD patients (Wunderli et al., 2016).

Substitute-agonist therapies mimic key aspects of the abused drug to reduce craving and withdrawal and promote abstinence (Herin et al., 2010). Research over the last decade has suggested that substitute agonist-based strategy can be useful in treating cocaine-use disorders (Mariani and Levin, 2007; Rothman, 2005). Chronic cocaine abuse is believed to result in depletion of dopamine. Dopamine deficiency has also been associated with ADHD in adults, and dopamine agonists have been effective in the pharmacotherapy of ADHD. Bromocriptine, a dopamine agonist was highly effective for treating ADHD and promoting cocaine abstinence (Grabowski et al., 2004). While the exact etiology of ADHD remains unknown, the available evidence supports the theory that dopamine neurotransmission dysfunction is at least partly responsible for its characteristic symptoms (Cocores et al., 1987).

Previously FDA has approved substitute-agonist therapies for substance-use disorders including methadone, buprenorphine, varenicline, and transdermal and buccal formulations of nicotine. Additionally, methylphenidate transdermal patch (Daytrana) has been successfully used for the treatment of ADHD (Mariani and Levin, 2007). It was the relative success of these

Abbreviations: ADHD, Attention-deficit/hyperactivity disorder; ANOVA, Analysis of variance; PBS, Phosphate buffered saline; PIB, Polyisobutylene; PSA, Pressure sensitive adhesives; RP-HPLC, Reverse phase high performance liquid chromatography; SE, Standard error; TDDS, Transdermal drug delivery systems

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medications for treatment of substance-use that stimulated initial research on potential of agonist medications to treat cocaine dependence (Silver, 2017). While there are currently no FDA-approved medications for cocaine dependence, agents that reverse dopamine transporter activity and boost dopamine transmission like amphetamines have shown promise. Dextroamphetamine and methamphetamine have shown to reduce cocaine use in patients with cocaine dependence alone, and mixed amphetamine salts have shown to reduce cocaine use in co-occurring cocaine dependence and ADHD. Dextroamphetamine and mixed amphetamine salts are FDA-approved treatments for ADHD, and are believed to work by boosting dopamine levels in the forebrain (Negus and Henningfield, 2014). Given these findings, we know both the disorders are linked to dopamine deficiency and can benefit from treatment with dopamine substitute agonists.

Although many targets for cocaine-use disorder have been identified, substitute agonists that function as substrate-based dopamine/norepinephrine releasers have demonstrated promising efficacy in preclinical models and double-blind placebo controlled clinical trials (Grabowski et al., 2004). 4-Benzylpiperidine is one such substrate-based dopamine/norepinephrine releasing substitute-agonist to cocaine with distinguished preclinical efficacy but has rapid onset of action and short duration of action. The value of an agonist medication lie in its ability to target pharmacological receptors to produce effects for a long duration of time with slower onset, and thereby, reducing cravings for drug of abuse while ensuring lower toxicity than produced by use of the abused drug. It is therefore critical to sustain the duration of action of 4-benzylpiperdine. Transdermal patches can provide this much needed slow and sustained delivery of 4-benzylpiperidine. Slow drug onset can reduce abuse potential, promote abstinence and prolonged duration of action can reduce the frequency of dosing leading to better compliance and reduce problematic neuroadaptations to the severe oscillations in drug levels that often occur with drug abuse. Further, transdermal patches can be abuse deterrent as it is harder and more time consuming to extract drug over conventional dosage forms (Puri et al., 2017).

Considering the prominent preclinical efficacy of 4-benzylpiperidine in human-relevant animal models and the therapeutic benefits of transdermal drug delivery of substitute agonists for cocaine-use disorder and ADHD, the aim of our study was to develop a drug-in-adhesive matrix transdermal patch of 4-benzylpiperidine. The objective was extended to evaluate the transdermal matrix patch based on the *in vitro* drug permeation profile across dermatomed human skin, and adhesion properties of the patch.

2. Materials and methods

2.1. Materials

4-Benzylpiperidine was obtained from Sigma Aldrich (St. Louis, MO, USA). Acetonitrile, methanol, tetrahydrofuran and Phosphate Buffered Saline (PBS) were purchased from Fisher Scientific (NJ, USA). Acrylate PSA (DURO-TAK 87-2516 and DURO-TAK 87-2287) as well as PIB adhesive (DURO-TAK 87-6908) were obtained as gift samples from Henkel Corporation (Dusseldorf, Germany). Silicone adhesive (BIO-PSA 7-4301) was also provided as gift sample by Dow Corning Corporation (Washington, DC, USA). Backing membranes (CoTran™ 9707, CoTran™ 9702, CoTran™ 9722, CoTran™ 9706, CoTran™ 9718 and ScotchPak™ 9723) and release liners (ScotchPak™ 9744, ScotchPak™ 1022 and ScotchPak™ 9741) were gifted by 3M (St. Paul, MN, USA). Isopropyl myristate, colloidal silicone dioxide, oleic acid, olely alcohol, propylene glycol and mineral oil were purchased from Sigma Aldrich (St. Louis, MO, USA). Dermatomed human skin was obtained from New York firefighters skin bank (New York, NY).

2.2. Methods

2.2.1. Development of transdermal patch

The choice of pressure sensitive adhesives (PSAs), release liner and backing membrane is critical for the development of a transdermal patch and were investigated extensively for the development of a 4-benzypiperidine drug-in-adhesive matrix transdermal patch.

2.2.1.1. Selection of PSA. Currently there are three types of pressure sensitive bioadhesive polymers commonly used in the United States transdermal drug delivery market: polyacrylate copolymers (acrylates), polysiloxanes (silicones) and polyisobutylenes (PIBs) (Kandavilli et al., 2002; Tan and Pfister, 1999). In our study, the feasibility of employing acrylate (DURO-TAK 387-2287 and DURO-TAK 387-2516), silicone (BIO PSA 7-4301) and PIB (DURO-TAK 87-6908) adhesives for the formulation of 4-benzylpiperidine drug-in-adhesive transdermal patches was tested. Slide crystallization studies were performed to identify the drug concentration at which the drug crystallizes or separates out. The highest concentration at which the drug remained dissolved, was considered as the drug's saturation solubility in each adhesive. Formulations with increasing concentrations of drug (% w/w) in adhesive were prepared (as presented in Tables 1 and 2) and allowed 48 h of slow mixing at room temperature using a rotary mixer (Preiser Scientific Inc., St. Albans, WV, USA). Following visual observation, a drop of each formulation blend was placed on individual polysine microscopic slides (25 × 75 × 1 mm, Thermo scientific, Erie scientific, New Hampshire, U.S.A) and dried under a fume hood at room temperature, followed by examination under an optical light microscope (Leica DM 750; Buffalo Grove, IL). Images were taken at 10× or 100× magnification (as specified) using a DFC-280 camera adjoining the microscope.

Table 1
Formulations prepared to test the solubility of 4-benzylpiperidine in the commonly used PSAs.

Adhesive	Contents (mg)	Drug (% w/w)			
		5	10	20	40
Acrylate (DURO-TAK 387-2287)	Adhesive wet weight	1120.00	1120.00	1120.00	1120.00
	Adhesive dry weight	565.60	565.60	565.60	565.60
	Amount of drug	29.77	62.84	141.40	377.07
Acrylate (DURO-TAK 387-2516)	Adhesive wet weight	1120.00	1120.00	1120.00	1120.00
	Adhesive dry weight	464.80	464.80	464.80	464.80
	Amount of drug	24.46	51.64	116.20	309.87
PIB (DURO-TAK 87-6908)	Adhesive wet weight	1120.00	1120.00	1120.00	1120.00
	Adhesive dry weight	425.60	425.60	425.60	425.60
	Amount of drug	22.40	47.29	106.40	283.73
Silicone (BIO PSA 7-4301)	Adhesive wet weight	1120.00	1120.00	1120.00	1120.00
	Adhesive dry weight	672.00	672.00	672.00	672.00
	Amount of drug	35.37	74.67	168.00	448.00

Table 2
Formulations prepared to further test the solubility of 4-benzylpiperidine in PIB and silicone adhesives.

Adhesive	Contents (mg)	Drug (% w/w)			
		5	10	20	40
PIB (DURO-TAK 87-6908)	Adhesive wet weight (mg)	1120	1120	1120	1120
	Adhesive dry weight (mg)	425.60	425.60	425.60	425.60
	Amount of drug (mg)	8.69	13.16	17.73	20.05
Silicone (BIO PSA 7-4301)	Adhesive wet weight (mg)	1120	1120	1120	1120
	Adhesive dry weight (mg)	672	672	672	672
	Amount of drug (mg)	13.71	20.78	28	31.66

2.2.1.2. Selection of additives. Penetration enhancers were explored to facilitate the delivery of 4-benzylpiperidine across skin and increase its solubility in the adhesives. The physical and chemical compatibility of isopropyl myristate, oleic acid, olely alcohol and mineral oil with the drug as well as the adhesives were tested. To determine the solubility of 4-benzylpiperidine in the enhancers, increasing amounts of 4-benzylpiperidine was added to the individual penetration enhancers, followed by mixing for 48 h in a rotary mixer. The solubility and stability of the enhancers in the adhesives were determined similarly, by adding increasing amounts of the enhancers to the adhesives, followed by mixing for 48 h in a rotary mixer. The adhesive blends were applied to individual polysine microscopic slides, dried under a fume hood at room temperature, and observed under an optical light microscope.

In addition, colloidal silicon dioxide was explored as a viscosity builder, and first homogenized to a gel with heptane using a high-speed homogenizer (OmniTHQ, Omni International, NW, GA, USA) at 32,000 rpm for 10 min. Varying concentrations of the gel, corresponding to the amount of colloidal silicon dioxide, were then added to the drug in silicone formulations (presented in Table 3), followed by evaluation with slide crystallization studies.

2.2.1.3. Selection of release liner and backing membrane. The following commonly used release liners: ScotchPak™ 9744, ScotchPak™ 1022 and ScotchPak™ 9741 and backing membranes: CoTran™ 9707, CoTran™ 9702, CoTran™ 9722, CoTran™ 9706, CoTran™ 9718 and ScotchPak™ 9723, were evaluated (Kandavilli et al., 2002). Combinations of the release liners and backing films were tested with the final drug-in-adhesive formulation blends (F-C-11, F-C-12, 10POA and 15POAOH). Initial screening was performed by checking the affinity of the formulations for both sides of each membrane, by adding a drop of the formulation on the membranes, followed by drying in a fume hood to evaporate the adhesive solvent. A gloved hand was used to test the peeling and adhesiveness of the formulations on individual membranes.

Table 3
Formulations prepared with 4-benzylpiperidine in silicone PSA along with additives (isopropyl myristate and colloidal silicon dioxide).

Formulations	Excipients (% w/w)			
	Drug	Silicone Adhesive (dry weight)	Isopropyl myristate	Colloidal silicone dioxide
F-C-4	10	72.5	10	7.5
F-C-5	5	82.5	5	7.5
F-C-6	5	77.5	10	7.5
F-C-7	12.5	70	10	7.5
F-C-8	10	75	5	10
F-C-9	12.5	72.5	5	10
F-C-10	10	77.5	5	7.5
F-C-11	10	80	0	10
F-C-12	5	85	0	10

2.2.2. Drug in adhesive patch preparation

The drug in adhesive transdermal patches were prepared by dissolving pre-determined amounts of drug, adhesive, and additives (presented in Table 5) into an air-tight glass vial (20-mL capacity) and stirred for 24 h using a rotary mixer. For the silicone adhesive based formulations, colloidal silicon dioxide was first homogenized into a gel as previously discussed, followed by the addition of the drug and the adhesive, which was then homogenized using a high shear homogenizer at 1200 rpm for 15 min. The silicone and PIB formulations were cast on individual release liners using a Gardner film casting knife (BYK-AG-4300 series, Columbia, MD, USA) and dried. The compositions, casting parameters, release liner, backing membrane, and drying conditions employed for the formulation of different patches have been elaborated in Table 5. Following drying, the sheets were laminated using individual backing membranes, which were placed on the cast films using a roller, ensuring no air pockets were formed. These laminated films were then die cut into drug in adhesive matrix transdermal patches of 2.83 cm^2. The patches were stored at room temperature for two weeks and observed under an optical light microscope. Visual changes including phase separation, contraction/shrinkage of the film, residue on release liner after peeling and ease of peeling off the patches were noted as well. Laminates without crystals and phase separation, with good physiochemical properties, were used for *in vitro* permeation studies on dermatomed human skin.

2.2.3. In vitro permeation

2.2.3.1. Skin preparation. Human dermatomed skin was stored at −80 °C and thawed before use in 10 mM PBS (pH 7.4) at 37 °C for 2 min. After thawing, skin was cut into pieces of appropriate sizes and their thickness was measured using a digital micrometer (Electronic Equip't Co. Inc, Cedarhurst, NY, USA). Skin pieces with comparable thickness values were used for further skin integrity studies.

2.2.3.2. Skin integrity testing. The barrier integrity of human dermatomed skin was evaluated by skin electrical resistance assessment. In this study, prepared skin pieces of appropriate thickness were clamped between the donor compartment containing 300 µL of 10 mM PBS and receptor compartment containing 5 mL of 10 mM PBS of a vertical Franz diffusion cell setup and allowed to equilibrate for 15 min. Silver chloride wire (load resistor R_L) was dipped in the donor chamber and silver electrode immersed in the

Table 4
Formulations prepared with 4-benzylpiperidine in PIB PSA along with additives (oleic acid and oleyl alcohol).

Formulations	Excipients (% w/w)			
	Drug	PIB Adhesive (dry weight)	Oleic Acid	Oleyl Alcohol
10POA	10	85	5	0
10POAOH	10	80	5	5
15POA	15	80	5	0
15POAOH	15	75	5	5

Table 5
Materials and conditions used to cast the drug in adhesive transdermal patches of 4-benzylpiperidine, and the observations made post two weeks of casting.

Patch		S1	S2	S3	S4	P1	P2
Components (% w/w)	Drug	10	10	5	5	10	15
	PIB Adhesive (% dry weight)	–	–	–	–	85	75
	Silicone Adhesive (% dry weight)	80	80	85	85	–	–
	Oleic Acid	–	–	–	–	5	5
	Oleyl Alcohol	–	–	–	–	–	5
	Colloidal silicone dioxide	10	10	10	10	–	–
Release liner		Fluoropolymer coated side of Scotchpak™ 9741	Fluoropolymer coated side of Scotchpak™ 9741	Fluoropolymer coated side of Scotchpak™ 9741	Fluoropolymer coated side of Scotchpak™ 9741	Polyester side of Scotchpak™ 9744	Polyester side of Scotchpak™ 9744
Backing membrane		Polyester side of Scotchpak™ 9723	CoTran™ 9718 (Polyethylene)	Polyester side of Scotchpak™ 9723	CoTran™ 9718 (Polyethylene)	Matte surface of Scotchpak™ 9723 (Polyethylene)	Matte surface of Scotchpak™ 9723 (Polyethylene)
Drying Conditions		A film of 15 mils in thickness was cast on the release liner and air dried in a fume hood for 2 min at room temperature, followed by drying at 75 °C for 15 min					
Observation after 2 weeks	Phase separation	✗	✗	✗	✗	✗	✗
	Ease of peeling	✓	✗	✓	✗	✓	✓
	Residue on release liner	✗	✓	✗	✓	✗	✗

receptor compartment. Skin resistance was measured by passing a constant current (voltage of 100 mV AC electrical field at 10 Hz, duty cycle 50% without offset) through skin using a Digital Multimeter (Agilent 34410A $6^{1/2}$ Digit) and Function/Arbitrary waveform generator (Agilent 33220A 20 MHz, Agilent Technologies, CA, USA). The voltage across the skin (V_s) was displayed on the multimeter and electrical resistance values were calculated using Eq. (1).

$$Rs = \frac{V_S R_L}{(V_0 - V_S)} \quad (1)$$

Where,

R_S represents skin electrical resistance (kΩ)
V_S represents the voltage drop across the skin (mV)
V_O represents the voltage drop across the whole circuit (100 mV)
R_L represents the load resistance (100 kΩ)

Skin pieces with resistance greater than 4 kΩ were selected for the studies. The resistance of all skin pieces chosen for the study ranged between 4 and 17 kΩ.

2.2.3.3. In vitro permeation studies using optimized patches. *In vitro* transdermal permeation studies were performed to evaluate the performance of the drug-in-adhesive transdermal patches, based on the amount of drug that permeates across human dermatomed skin over 48 h using vertical Franz diffusion cells (PermeGear V6 station vertical cell). Three different matrix transdermal patches (S1, P1 and P2) with four replicates (n = 4) were tested for their *in vitro* transdermal permeation performance. Transdermal patches, large enough to cover the Franz cells were punched using a die and the release liner was removed. The patches were placed on the skin, dried using kim wipes, such that the adhesive side of the patch was in contact with the stratum corneum of the skin. A glass rod with minimal pressure was rolled over the patch to ensure the patch is in complete contact with the skin. The skin with the matrix patch was immediately placed over the surface of the receptor compartment, followed by clamping of skin with patch between the donor compartment and receptor compartment. The receptor comprised of 10 mM PBS (pH 7.4) maintained at 37 °C and constantly stirred at 600 rpm. The donor chamber was exposed to room temperature (25 °C) to attain a skin temperature of 32 °C. Samples (300 μL) were withdrawn from the receptor compartment at zero time, 1 h, 2 h, 4 h, 6 h, 8 h, 24 h and 48 h and quantified using RP-HPLC (reverse phase high performance liquid chromatography). Equal amount of 10 mM PBS (pH 7.4) was replenished in the receptors.

2.2.3.4. HPLC quantification. A RP-HPLC Waters 2695 Separation Module attached to a Waters 2996 photodiode array detector connected to a prodigy 5 μ ODS (150 mm length × 4.60 mm diameter, 5-μm particle size) column were used for the quantitative analysis of 4-benzylpiperdine. Acetonitrile and deionized water (0.05% v/v TFA) in gradient mode and flow rate of 1.0 mL/min were employed as the mobile phase. The percentage of acetonitrile was increased from 10% to 80% from 0 to 8 min, then kept at 80% till 13 min, followed by a decrease to 10% at 13.01 min and maintained at 10% till 15 min (end of the run). 4-Benzylpiperidine was detected at 259 nm wavelength with a retention time of 5.5 min.

2.2.3.5. Data analyses. All values have been presented as mean ± SE. One-way ANOVA was performed to investigate significant difference between groups. Statistically significant difference was shown by p values < 0.05.

2.2.4. Characterization of the optimized drug in adhesive patch

The transdermal matrix patch that exhibited the highest drug permeation across dermatomed human skin in 48 h was elected as the final patch and further characterized.

2.2.4.1. Determination of coat weight. The coat weight of the drug in adhesive patch was determined by punching (using a die cut) and weighing 0.28 cm^2 of the laminates (adhesive matrix with backing membrane and release liner) and subtracting the weight of the backing membrane and release liner (n = 6). The average weight of the patch along with the standard error was reported.

2.2.4.2. Peel adhesion test. The bond strength of the optimized patch (P2) was determined using a PA-1000-180 180° peel adhesion tester (Chem Instruments, Fairfield, OH, USA). The force required to pull the patch away from a non-flexible material (stainless steel), that is positioned parallel to the patch, was quantified. The instrument was calibrated prior to use and setup at a speed of 30 cm/min and a peel length of 0.5. Rectangular strips of the patch were cut to the size of 6.35 × 1.5 cm (n = 6) and used for this test. One end of the test strip was placed in the load cell grip and the other end was made to adhere to the test platform. The average force required to peel the patch from the stainless steel was determined and recorded.

2.2.4.3. Shear strength. Sheer strength of the patch was tested using a SS-HT-8 High Temperature 8 Bank Shear Tester (Chem Instruments, Fairfield, OH, USA). All patches were cut into 2 cm wide and 8 cm long strips. The liner was removed from one end and patch was applied on the test panel of shear tester such that 5 cm long strip is stuck on to the test panel with a 3 cm attaching length. The other end was attached with hooks and weight (500 g) was applied on the hook. The time required for the patch to fall was recorded and repeated for six replicates.

2.2.4.4. Tack testing. A TA.XTPlus Texture Analyzer (TTC, Hamilton, Massachusetts, USA) was used to determine the tack value of the final drug-in-adhesive patch, P2. The texture analyzer was calibrated for weight, height, and a distance of 50 mm. The patch was cut to an appropriate size and the release liner was removed such that the adhesive part of the patch could be stuck onto the TA-303 Indexable Tack Rig with ten 9 mm openings. The stainless-steel probe was then lowered into the 9 mm openings of the indexable tack rig and a constant force of 0.05 N was applied onto the sample for 5 s and, finally, the probe was removed with a constant rate. The debonding velocity (Vd) was set to 5 mm/s. The absence of PSA residues from the stainless-steel surface of the probes (adhesive failure) was visually determined. The absolute positive force required for debonding is recorded along with the positive area and separation distance. Exponent texture analysis software was used to measure the detachment force (absolute positive force) and the elongation at break (separation distance) expressed in grams and millimeters, respectively. The results are expressed as the mean ± standard error (n = 6).

3. Results and discussion

3.1. Development of the transdermal patch

Transdermal drug delivery systems (TDDS) are employed for the delivery of drugs across skin, into the systemic circulation. Adhesion of a TDDS to skin is a critical factor that affects its performance. The entire delivery surface of a TDDS must be in complete contact with skin, as the partitioning of the drug between the TDDS and skin is the driving force for permeation. In transdermal patches, the adhesiveness of the PSA helps maintain this intimate contact with skin. Apart from adhesion, the PSA also affects other critical quality attributes of the TDDS such as drug delivery, flux across skin and physical and chemical stability, making it critical to the safety, efficacy and quality of the finished product. The selection of a suitable PSA is thus pivotal in the development of a transdermal patch (Deepthi and Khan, 2012; Lobo et al., 2016). In our study we employed solubility and crystallization studies to aid us choose the most appropriate PSA for our drug.

The three most commonly used PSAs i.e. acrylates, silicone and PIB base adhesives were all used in this study. Initial blends prepared (as presented in Table 1) were observed visually, indicating that the solubility of 4-benzylpiperidine was the highest in the acrylate adhesives (greater than 20% w/w in DURO-TAK 387-2516 and greater than 10% w/w in DURO-TAK 387-2287). However, color change in the soluble blends indicative of degradation or incompatibility of 4-benzylpiperidine as well as formation of crystals on drying with the acrylate adhesives was observed (presented in Fig. 1). Hence, further studies using the acrylate PSAs were discontinued.

The solubility of 4-benzylpiperidine in silicone and PIB adhesives was found to be lower than 5% w/w. Blends were prepared in accordance to Table 2, and the solubility of 4-benzylpiperidine in silicone and PIB was found to be less than 4.5% w/w. Slide crystallization was used as a preliminary and relatively fast screening tool to mimic the nature of the final casted laminate and the interaction between the drug and adhesive in the final product. It was employed as an alternative to preparing complete patches (Jain and Banga, 2013). These studies revealed no crystal formation, degradation, or separation over time in the drug in PIB blends (4.5%, 3%, 2% w/w drug). Thus, PIB was further developed into a transdermal patch of 4-benzylpiperidine. Slide crystallization studies in all the blends prepared with silicone adhesive showed separation of the 4-benzylpiperidine from the dried silicone matrix (shown in Fig. 1). However, as no degradation of 4-benzylpiperidine or any physical incompatibility in terms of color change or the formation of crystals was observed, silicone PSA was also further explored for the development of the 4-benzylpiperidine transdermal patch.

In our study, permeation enhancers were explored to prevent phase separation observed in drug in silicone formulations, increase the solubility of drug in both silicone and PIB PSAs to allow more drug loading into the patch, and subsequently increase the penetration of drug across skin. Isopropyl myristate, propylene glycol, mineral oil, oleic acid and olelyl alcohol were evaluated, as 4-benzylpiperidine was found to be the most soluble in these enhancers after an initial preliminary screening of commonly used permeation enhancers. Preliminary screening involved adding increasing amounts of the permeation enhancers to the drug and adhesives blends, followed by visual and microscopic observation. Among these, isopropyl myristate showed higher miscibility with silicone PSA, while oleic acid and olelyl alcohol were better miscible with PIB PSA. Consequently, isopropyl myristate was tested as a solubility and penetration enhancer for the drug in silicone blends whereas, oleic acid and olely alcohol were incorporated in the drug-in-PIB blends.

Silicone adhesive blends with isopropyl myristate (5% and 10% w/w) and increasing concentrations of 4-benzylpiperidine (5%, 10% and 12.5% w/w) were prepared, and slide crystallization studies were performed. The addition of 10% w/w isopropyl myristate led to incorporation of higher concentration of drug (up to 10% w/w) without separation from the dried adhesive blend, confirmed by slide crystallization studies. The concentration of isopropyl myristate was limited to 10% w/w based on the inactive ingredient guide provided by FDA (U.S. Food & Drug Administration, 2018). The incorporation of liquid components (drug and permeation enhancer) in the silicone PSA led to a decrease in the viscosity of the formulation blends. Therefore, the addition of a viscosity enhancer was considered to lower the fluidity of the blend, enabling the formulation to be cast as a film. Previous literature demonstrates the successful use of colloidal silicone dioxide as a viscosity enhancer (Enscore and Gale, 1985). Direct addition of colloidal silicone dioxide to the adhesive blend led to the formation of indispersible lumps in the blend. Hence, prior to addition, colloidal silicone dioxide was homogenized to a gel which could be incorporated uniformly into the adhesive. The percentage of colloidal silicone dioxide remaining in the gel after exposing it to the processing conditions of the patch was evaluated each time during preparation of an adhesive blend, and the wet weight of gel to be added was back-calculated accordingly.

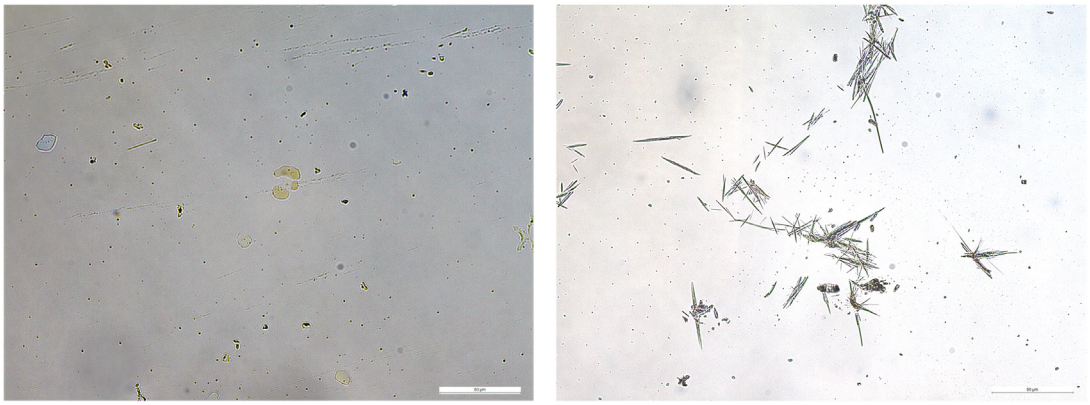

Fig. 1. Brightfield microscopic image showing (a) separation of drug (5% w/w) from dried silicone adhesive and (b) formation of crystals in dried acrylate (DURO-TAK 387-2516) adhesive. Scale bar = 50 µm.

Formulations F-C-11 and F-C-12, containing 10% w/w colloidal silicone dioxide and devoid of isopropyl myristate, were found to be the most suitable for the preparation of a transdermal patch. A loss in adhesive properties of the dried matrix was observed in the formulations containing isopropyl myristate. Therefore, the use of isopropyl myristate for drug in silicone blends was omitted. Colloidal silicone dioxide at 10% concentration prevented the separation of drug for the dried adhesive matrix, while retaining the adhesive property of the dried matrix and eliminated the need of adding isopropyl myristate.

Oleic acid and oleyl alcohol are also well-known chemical penetration enhancers that were included in the PIB adhesive blends (Burton and Tata, 1999; Naik et al., 2000). Based on preliminary solubility studies and existing literature recommendations, the concentration of oleic acid, oleyl alcohol was limited to 5% w/w individually or 10% w/w in combination (Govil et al., 1993). On microscopical evaluation, a uniform dispersion of drug as droplets was observed on for formulations 10POA, 10POAOH and 15POAOH (presented in Table 4). The matrix was found to be stable, with no apparent coalescence of the droplets over a period of two weeks from casting on a slide. In case of 15POA, phase separation of drug from the dried matrix was observed. The addition of oleic acid was successful in preventing the separation of up to 10% w/w 4-benzylpiperidine, which led to a higher drug loading in the formulation. Formulations 10POA and 15POAOH were further investigated for the development of a transdermal patch of 4-benzylpiperidine.

Drug in adhesive transdermal systems have three layers: backing film, a drug in adhesive matrix layer and protective release liner. The backing film serves as the outer surface of a patch and prevents direct contact of the patch formulation with the environment. Additionally, it provides mechanical support and physical integrity to the transdermal system while also being compatible with the drug, adhesive and excipients of the formulation. Release liners act as a protective layer for the transdermal patch system during the product shelf life and act as substrates for the coating process therefore, they must be selected to provide consistent release performance and inertness in the end-use application (Kandavilli et al., 2002). Adhesive formulations can vary widely containing various additives, which can impact release performance and adhesion properties. Considering the many factors involved, evaluation of several release liners and backing is critical for the development of a transdermal patch (Govil et al., 1993; Wokovich et al., 2011). In the present study, the final formulation blends selected (F-C-11 and F-C-12 silicone PSA based formulations; 10POA and 15POAOH PIB based formulations) were tested with a range of commonly used membranes, used as release liners and backings. The material for release liner for the individual blends was chosen such that the dried formulation would peel off easily from it, leaving no residue behind. On the contrary, the membranes with great affinity for the formulation were chosen as backing membranes. Consecutively, transdermal patches of these formulations were prepared with the most suitable combination of release liner and backing (as described in Table 5). For the formulations containing silicone PSA, fluoropolymer coated membranes were chosen as the release liner and polyester or polyethylene-based membranes were found to have a greater affinity for the formulation and selected as backing. For the PIB based formulations, polyester was chosen for the release liner and polyethylene as backing.

3.2. Drug in adhesive patch preparation

Drug in adhesive transdermal patches of 4-benzylpiperidine, with PIB and silicone PSAs were developed successfully (summarized in Table 5). None of the patches developed showed separation of 4-benzylpiperidine from the dried laminate or the formation of crystals when observed under an optical microscope over two weeks. However, patches S2 and S4 had problems in terms of peeling, where the laminate did not transfer entirely to the backing membrane and left residue on the release liner. As S1 had higher concentration of drug than S3, patches S1, P1 and P2 were further tested for their drug permeation profiles.

3.3. In vitro permeation

The average cumulative amount of 4-benzylpiperidine that permeated across dermatomed human skin, over 48 h, from S1 silicone adhesive patch, P1 drug-in-PIB adhesive patch and P2 drug-in-PIB

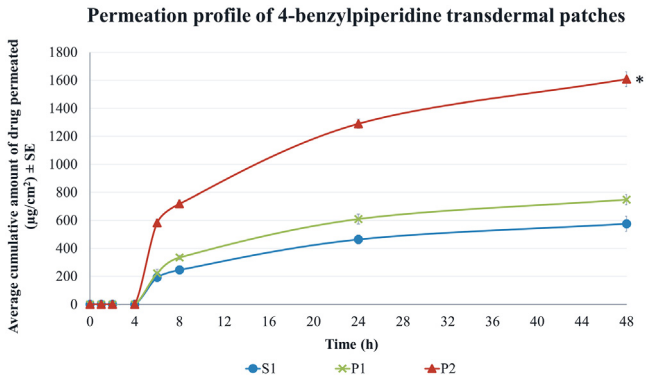

Fig. 2. Demonstrates the *in vitro* permeation profile of 4-benzylpiperdine from the three patches tested across human dermatomed skin over 48 h. *Represents statistical difference ($p < 0.05$).

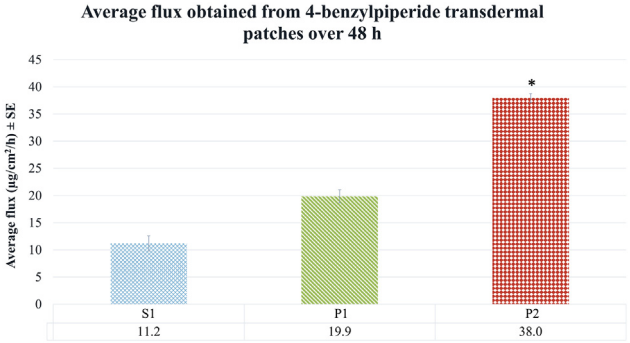

Fig. 3. Demonstrates the average flux obtained from the three patches tested (S1, P1 and P2) at the end of 48 h. *Represents statistical difference when ($p < 0.05$).

adhesive patch were found to be 559.2 ± 79.4 µg/cm^2, 748.1 ± 36.0 µg/cm^2, and 1608.5 ± 53.4 µg/cm^2 respectively. Patch P2 demonstrated significantly higher *in vitro* drug permeation compared to the other two patches, as shown in Fig. 2. The average flux of 4-benzylpiperidine from S1, P1 and P2 was found to be 11.2 ± 1.4 µg/cm^2/h, 19.9 ± 1.2 µg/cm^2/h, and 38.0 ± 0.8 µg/cm^2/h respectively, where the highest flux was obtained from P2, as shown in Fig. 3. The higher permeation of 4-benzylpiperidine from patch P2 can be attributed to the higher drug loading (15% w/w) as well as the addition of two permeation enhancers, oleic acid and oleyl alcohol. To obtain maximum delivery of 4-benzylpiperidine, patch P2 was selected as the final transdermal patch of 4-benzylpiperidine.

3.4. Characterization of the optimized drug in adhesive patch

Patch P2 was further characterized as the final transdermal patch of 4-benzylpiperidine.

3.4.1. Determination of coat weight

The coating efficiency of a transdermal patch can be determined by measuring the coat weight of different regions of the laminate. The variation in coat weight can be attributed to non-volatile components in the adhesive blend (European Medicines Agency, 2014). The average weight of patch P2, excluding the weight of the release liner and backing membrane, was found to be 4.1 ± 0.6 mg, indicating uniformity in coat weight throughout the laminate.

3.4.2. Peel adhesion test

An ideal transdermal patch should peel off without causing delamination. Peel resistance is not only dependent on the intrinsic adhesiveness of the PSA but is a complex process that involves the extension and the bending of the patch matrix and the backing layer prior to separation. The force required to peel the patch was kept consistent and as the value of peel adhesion is affected by the width of the sample, the size of the patches were kept constant (Cilurzo et al., 2012). The average force required to peel patch P2 from stainless steel was found to be 0.7 ± 0.2 g. There was no delamination on the stainless steel for the tested transdermal patches.

3.4.3. Shear strength

Shear adhesion reveals the resistance of a transdermal patch to tangential stresses and, therefore, the cohesion of the matrix (Cilurzo et al., 2012; Leong et al., 2003). In this study, the parallel force required to pull a fixed area of the patch (15 cm^2) from a standard flat surface (stainless steel) was tested. The average time taken for the patch to drop from the test surface was found to be 53.8 ± 7.9 s.

3.4.4. Tack testing

The adhesion efficiency of a transdermal patch can be tested by tack evaluation methods, which measure the force of debonding on application of a light pressure, for a short duration of time. A probe tack test was employed in this study, where the force required to separate a probe from the adhesive surface of a transdermal patch was measured. In this method, tack is expressed as the maximum value of the force required to break the bond between the probe and transdermal patch after a brief period of contact (Cilurzo et al., 2012). The average absolute positive force, average positive area and average separation distance, recorded for six replicates, was found to be 80.4 ± 11.9 g, 5.2 ± 1.0 g/s and 0.9 ± 0.0 mm respectively.

4. Conclusion

Based on our results, the development of a transdermal drug-in-adhesive patch of 4-benzylpiperidine was successful with silicone based and PIB based PSAs. Solubility and slide crystallization studies demonstrated incompatibility of acrylates PSAs with the drug, hence, silicone and PIB PSAs were selected for further patch development. The use of oleic acid, oleyl alcohol and isopropyl myristate was found to be beneficial in increasing the loading of the drug in the patches as well as permeation enhancers. In addition, colloidal silicone dioxide was successfully incorporated in the silicone-based patches as a viscosity-building agent. Fluoropolymer coated membranes as the release liner and polyester or polyethylene-based membranes as backing were chosen to develop the silicone PSA based drug in adhesive patches. Among these S1 showed superior peeling performance and had higher drug loading. For the PIB based formulations, polyester was chosen for the release liner and polyethylene as backing. Patches S1, P1 and P2 were further evaluated for their drug permeation profiles across dermatomed human skin. Higher delivery of drug from the two PIB based transdermal patches over the silicone-based transdermal patch was obtained, and the P2 PIB based PSA transdermal patch was selected as the final patch for further evaluation of adhesive properties. The final patch demonstrated uniformity in coat weight, peel adhesion, tack test and shear strength. Further studies to evaluate the *in vivo* performance of the optimized transdermal patch however will be required.

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