Introduction

Oral drug delivery is the most common route for its convenient and easy administration in Bangladesh. But, it has several limitations such as the hepatic first pass effect, enzymatic degradation and inactivation in gastric environment. Another, hypodermic needles are painful, less convenient and expensive for patients [1]. However, current drug delivery technologies are facilitated by either (trans) mucosal [2-5], or transdermal [6] delivery system. The mucosal route of drug administration has some additional advantages, showing the low enzymatic activity, painless delivery that improved patient compliance, easy termination of dosage form, option to incorporate permeation enhancer and flexibility in developing fast or controlled release systems for systemic or non-systemic effect [7-9]. Moreover, it can be beneficial for patients who have complexity in swallowing tablets or capsules. Also, the drug release is characteristically related to the physicochemical properties of drugs in the aqueous medium [10].

In these circumstances, it was necessary to develop an alternative drug delivery system, in order to overcome these limitations related to the oral drug delivery and injections. In this research work, doxycycline was chosen as a model antibiotic from tetracycline group that showed it activity against wound infections. The formulations were prepared by using mucoadhesive polymer (hydroxypropyl methyl cellulose), cellulose gum (sodium carboxymethyl cellulose)/ instant release film former (Kollicoat®) - a polyvinyl alcohol/polyethylene glycol graft copolymer and plasticiser (glycerol). Preliminary studies were carried out for weight uniformity, percentage moisture content and uptake, folding endurance, elongation, swelling index, surface pH, hydration time and in vitro release studies using modified Franz Diffusion Cells. Concentration of different polymers was tailored by the release rate of doxycycline from the films. In conclusions, inkjet printing can be a key tool for the manufacture of thin films for the treatment a wide range of bacterial wound infection.

Keywords: Inkjet printing; Wound infection; Thin film; Doxycycline; Transdermal film
was cleaned according to the standard cleaning methods. Word 2013 (Microsoft Inc.) was employed for the printing of DC-loaded films. The sizes of the films were adjusted to 27 mm x 15 mm in size after final cutting procedures. Each printed film was allowed to dry at room temperature for 1 hour before printing of another layer (total 5 printed cycle). The compositions of blank- and DC-loaded formulations are shown in Table 1.

**Table 1**: Optimized blank- and drug-loaded thin films prepared with different amounts of polymers and plasticizer.

| Formulation | Polymers: Plasticizer | Weight Ratios (w/w) | DC (% w/w) |
|-------------|------------------------|---------------------|------------|
| F1          | HPMC: NaCMC: GLY       | 0.9:0.1:1           | 4.8        |
| F2          | HPMC: KOL: GLY         | 0.9:0.1:1           | 4.8        |
| F3          | HPMC: KOL: GLY         | 0.8:0.2:1           | 4.8        |

**Physicochemical characterisations**: Printed films were peeled off from backing layer sheet using flat tip tweezers. Each film was weighed for weight uniformity using digital balance (Shimadzu Co. Limited, Japan). All experiments were carried out in triplicate. For the measurement of moisture content, Individual weight of each film was taken and held in a desiccators containing calcium chloride granules for 24 hours at room temperature. After 24 hours, films were re-weighed again. The percentage (%) moisture content of each film was determined using following equation [11]:

\[
\text{% Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100
\]

To calculate the moisture uptake, each film was kept in saturated solution of potassium chloride (84% relative humidity) for 24 hours. Moisture content and uptake were investigated in triplicate for each formulation. The percentage (%) moisture uptake was determined from following equation [11]:

\[
\text{% Moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100
\]

Consequently, an agar plate (2% w/v) was prepared for the measurements of surface pH and swelling studies for DC-loaded films (n=3). A digital pH meter (Hanna Instrument Inc., USA) was used to measure the pH after putting the films in an incubator maintained at 37±0.2°C. Swelling studies of the films were also measured after hour, following same temperature as pH measurement. The equation involved in calculation of swelling is given below [12-14]:

\[
\text{Swelling studies} = \frac{W_s - W_d}{W_d} \times 100
\]

Where \(W_d\) = Dry weight of thin film, \(W_s\) = Weight of film after swelling.

Percent elongation study is necessary to examine the stress that a film can hold. The percent elongation of the films was calculated using the following formula [11]:

\[
\text{Percent Elongation} = \frac{L_x 100}{L_o}
\]

Where, \(L_x\) = Increase in length of thin film, \(L_o\) = Initial length of film.

Folding endurance of the films was determined manually for films. It was counted when a film folded at a fixed position till it fractures [7,15]. Hydration studies require form imicking or predicting the full wetting time of each film. A hydration study of each film was carried out in 50ml of phosphate buffer saline (P.B.S) pH 7.4 at a rotation per minute till complete dissolution achieved. The buffer solution was prepared using KHPO4 and NaOH (0.1M) to get a pH of 7.4 equivalent to blood plasma condition [7,16].

**In vitro drug release studies**: The in vitro permeation study of DC was studied into the full thickness mice skin tissue (thickness ≤500 µm) using modified Franz Diffusion cell (Anton Scientific Limited, India) in P.B.S pH 7.4 at 37°C. Sample (2ml) was collected at planned intervals (0-60 minutes), from the sampling compartment and analysed at 240nm using UV-spectrophotometer (Boekel & Co., Hamburg, Germany).

**Statistical analysis**: The data are presented as the mean ± standard deviation (SD) and the results were analyzed via student’s t test. Statistical significance is indicated as for \(p < 0.05\).

**Results**

The aim of the research work was to develop and characterise DC loaded thin film using inkjet printing technology. Firstly, an inkjet printing method was optimised for the development of thin film with minimum loss of materials. Secondly, this study was carried out on the basis of two factors, namely selection of an appropriate amount of HPMC, NaCMC/KOL and GLY for the development of optimised film, followed by the physicochemical characterisations of films. For all film formulations, GLY (1%) w/w was added to the solution for preparing more flexible and elastic film without any brittleness. The average drying time for the films were 60mins at a temperature not exceeding 25°C. Figure 1 shows the digital photographs of thin films (27mm X 15mm), prepared during this research work. All films were investigated for the physicochemical characteristics such as weight uniformity, moisture content and uptake, surface pH, swelling studies, elongation, folding endurance and hydration studies. As it can be seen from Table 2, weight of each film (0.10-0.13g) confirmed the reliable and reproducible data though it was cut manually by stainless steel cutter. It was evident from moisture content and uptake studies, hydrophilic drug (DC) and polymers (HPMC/NaCMC/KOL) have a great ability to content (F3>F2>F1) and uptake moisture (F1>F2>F3) from the environment. Surface pH of the films was in the range between 7.2-7.75 which is similar to the transdermal environment. The swelling studies of DC loaded films were carried out for an hour in an agar medium (2%) w/v at 37°C in an oven for maintaining the same temperature as human body. In the findings, all of the films were dissolved completely (100%) within 30mins for hydrophilic drug and polymers, ability to swell. Plasticizer has a direct influence on the plastic or elongation properties of each thin film. The films showed the...
Inkjet Printing of Doxycycline Loaded Transdermal Film for Wound Infection

practical folding endurance which was not more than 129 (±3.0) times in number and no observable fractures. Folding endurance of the films was represented as F3>F1>F3. HPMC, NaCMC/KOL and GLY influenced the folding endurance of the film, high the ratios of plasticiser exhibit upper folding endurance.

To study the release profile of DC into the mice skin tissue, DC loaded films were carried out into PBS of pH 7.4 and the cumulative release profile for each film was studied for 30mins using modified Franz Diffusion cells. DC was selected in order to examine the effect of the polymers-drug combination. Figure 2 demonstrates the release of the DC where the increase of HPMC ratio, resulted in slower release rates for F1 and F2. The release rates were 68.9% and 80.6% being released after 20mins for F1 and F2 while faster release was observed for F3 (98.2%). After 30 minutes, all films showed complete release of DC in the simulated blood fluid media via skin tissue. The DC release patterns are considerably faster rate from F3, most probably because of the higher water solubility of DC, HPMC and KOL. Also, KOL is a higher molecular and instant release film forming polymer that might influence in the release of DC. However, DC release rates were significantly lower at the beginning, until the full hydration of film into the skin.

Table 2: Physicochemical characterizations of thin films (Mean±SD).

| Formulation | Weight (g) | % Moisture Content | % Moisture Uptake | Surface pH | % Swelling Index | % Elongation | Folding Endurance (Number) | Hydration Time (Min) |
|-------------|------------|--------------------|-------------------|------------|-----------------|--------------|----------------------------|---------------------|
| F1          | 0.12±0.01  | 18.1±0.5           | 17.8±2.8          | 7.3±0.1    | 100±0.0         | 7.4±0.8      | 121.0±3.0                  | 10-May              |
| F2          | 0.12±0.01  | 22.4±0.3           | 8.10±2.5          | 7.4±0.1    | 100±0.0         | 7.2±1.2      | 129.0±3.0                  | 10-May              |
| F3          | 0.12±0.00  | 25.4±0.7           | 4.00±1.1          | 7.3±0.1    | 100±0.0         | 8.7±1.5      | 113.0±4.0                  | 5-Feb               |

Discussion

The primary objectives of this investigation was to prepare uniformed DC loaded thin films using biocompatible materials approved by the Food and Drug Administration (FDA) with maximum loading of DC. Unfortunately, oral drug delivery systems possess a key limitation explicitly lack of bioavailability due to first-pass metabolism [4]. However, film was used for the relief of discomfort and fear of injection in paediatric and geriatric community [17]. KOL (MW: 45 kDa) might entrap air bubbles that might have some effects on the physicochemical properties and in vitro and in vivo drug release across the mice skin. To overcome the technical error for complete hydration without trapped air bubble, a lower temperature with less stirring was used to reduce the air bubble formation [18]. This research work consider as a proof of concept and the key purpose was to find out the possibility of administering therapeutically relevant doses of DC using thin films. Furthermore, lower the content of water was probable reason for the brittleness of the film at higher concentration of polymer [7]. Plasticizer, such as glycerol was used to decrease film brittleness. However, the physicochemical properties were not affected by drying time of the films. The principal examinations were carried out for the transparency, plasticity and thickness [19]. An acidic or alkaline pH may irritate the skin and affect the degree of polymer hydration [14]. The DC-loaded films were dissolved in between 2-10 minutes. The in vitro permeation studies of DC, was investigated with films across mice skin using modified Franz diffusion cells revealed that 98.2% (p < 0.05) of DC loadings were successfully delivered in 30 minutes. Also, the fresh buffer medium was added at various intervals to maintain sink condition [20].
Inkjet Printing of Doxycycline Loaded Transdermal Film for Wound Infection

Conclusion

In conclusion, inkjet printing was used to print the thin films with various ratios of HPMC and NaCMC/KOL with doxycycline and successfully released from the films. The films were uniform, reproducible and accurate in relation to physicochemical characterization and drug release profile. The hydrophilic drug, doxycycline, showed fast release profiles with most of the combinations, released within an hour. This release phenomenon was achieved not only with HPMC but mostly with KOL, a polymer with high solubilising capacity, which increased the drug release rates. Film dosage form is a new technology for delivering a wide range of active pharmaceutical substances compared to conventional approaches and can be further used for encapsulated protein and peptide delivery.

Acknowledgment

None.

Conflict of Interest

None.

References

1. Uddin MJ, Sultana I, Nipa AA, Chowdhury MM, Douroumis D (2016) Future drug delivery technologies: Bench top to industry. 10th International Conferences on Innovations in Science, Engineering & Technology; Chittagong; Bangladesh.
2. Ammar HO, Ghorab MM, Mahmoud AA, Shahin HI (2017) Design and In Vitro/In Vivo Evaluation of Ultra-Thin Mucoadhesive Buccal Film Containing Fluticasone Propionate. AAPS Pharm Sci Tech 18(1): 93-103.
3. Bai SA, Xiang Q, Finn A (2016) Evaluation of the Pharmacokinetics of Single-and Multiple-dose Buprenorphine Buccal Film in Healthy Volunteers. Clin Ther 38(2): 358-369.
4. Bilbault T, Taylor S, Walker R, Grundy SL, Pappert EJ, et al. (2016) Buccal mucosal irritation studies of sublingual apomorphine film (AFL-130277) in Syrian golden hamsters. Ther Deliv 7(9): 611-618.
5. Kalia V Garg T, Rath G, Goyal AK (2016) Development and evaluation of a sublingual film of the antiemetic granisetron hydrochloride. Artif Cells Nanomed Biotechnol 44(3): 842-846.
6. Uddin MJ, Scoutaris N, Klepetsanis P, Chowdhry B, Prausnitz MR, et al. (2015) Inkjet printing of transdermal microneedles for the delivery of anticancer agents. Int J Pharm 494(2): 593-602.
7. Boateng J, Mani J, Kianfar F (2013) Improving drug loading of mucosal solvent cast films using a combination of hydrophilic polymers with amoxicillin and paracetamol as model drugs. BioMed Research International 2013: 8.
8. Boateng JS, Okeke O (2014) Chitosan-based films for the sustained release of peptides: a new era in buccal delivery? Ther Deliv 5(5): 497-500.
9. Navamanisubramanian R, Nerella R, Chamundeesswari D, Seetharaman S (2017) Use of Okra Mucligae and Chitosan Acetate in Verapamil Hydrochloride buccal patches development; In vitro and Ex vivo Characterization. Journal of Young Pharmacists 9(1): 94-99.
10. Murata Y, Kofuj K, Maida C (2016) Control of Drug Dissolution Rate from Film Dosage Forms Containing Valsartan. Int Sch Res Notices 2016: 5135173.
11. Madhavi BR, Murthy VS, Rani, AP Kumar GD (2013) Buccal Film Drug Delivery System-An Innovative and Emerging Technology. Journal of Mol Pharm Organ Proc Res 1: 107.
12. Nair AB, Kumra R, Harsha S, Atimmarad M, Al-Dhubiab BE, et al. (2013) In vitro techniques to evaluate buccal films. J Control Release 164(1): 10-21.
13. Perioli L, Ambrogi V, Angelici F, Ricci M, Giovagnoli S, et al. (2004) Development of mucoadhesive patches for buccal administration of ibuprofen. J Control Release 99(1): 73-82.
14. Wu W, Chen W, Jin Q (2016) Oral mucoadhesive buccal film of ciprofloxacin for periodontitis: preparation and characterization. Trop J Pharm Res 15(3): 447-451.
15. Khana R, Agarwal SP, Ahuja A (1997) Preparation and evaluation of muco-adhesive buccal films of clotrimazole for oral Candida infections. Indian J Pharm Sci 59(6): 299-305.
16. Shende PK, Gaud RS, Bakal R, Yeole Y (2016) Clove Oil Emulsified Buccal Patch of Serratiopeptidase for Controlled Release in Toothache. J Bioequiv Availab 8: 134-139.
17. Roh J, Han M, Kim KN, Kim KM (2016) The in vitro and in vivo effects of a fast-dissolving mucoadhesive bi-layered strip as topical anesthetics. Dent Mater J 35(4): 601-605.
18. Rosen MR (2005) Delivery system handbook for personal care and cosmetic products: Technology, applications, and formulations. William Andrew Publishers Inc., Norwich, UK, pp. 120-124.
19. Boateng JS, Matthews KH, Stevens NN, Eccleston GM (2008) Wound healing dressings and drug delivery systems. J Pharm Sci 97(8): 2892-2923.
20. Kianfar F, Chowdhry BZ, Antonijevic MD, Boateng JS (2012) Novel films for drug delivery via the buccal mucosa using model soluble and insoluble drugs. Drug Dev Ind Pharm 38(10): 1207-1220.