INVESTIGATION OF POTENTIAL ABILITY OF NOVEL BIOPOLYMER MATRIX FOR DEVELOPMENT OF TRANSDERMAL DRUG DELIVERY VEHICLE

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INTRODUCTION

There are various types and mechanisms available currently to deliver a drug to our body. Drug delivery systems (DDS) are engineered technologies for the targeted delivery and or controlled release of therapeutic agents. Transdermal drug delivery systems (TDDS) have gained higher attention among these DDS. Nowadays, lots of novel materials have been invented which shows the potential to use as drug delivery systems.

The existing TDDS are showing some major drawbacks such as short half life time, limiting only to potent drug molecules and causing skin irritations or sensitization. Therefore, it is very essential to introduce biocompatible and potential material to overcome these problems. The biopolymer is one of the promising materials which can be used as TDDS. When considering the biopolymer based TDDSs major problems that arise are less ability to maintain a unique dispersion of the drug throughout the biopolymer matrix and high cost of biopolymer synthesis. Therefore, the specific objectives of this study were to develop a novel biopolymer matrix to overcome the above drawbacks and to develop a novel biopolymer based controlled release drug delivery system for the pharmaceutical and cosmetic industry. These biopolymers can preserve drug concentration by controlling the rate of drug release and reduces side effects by releasing the drugs at target cells (Sonawane et al., 2014, Panda & Suresh, 2015, Kawsar et al., 2010).

The main objectives of this research work are to develop a novel biopolymer based controlled release drug delivery system for pharmaceutical and cosmetic industry. Therefore, under this investigation a novel inert biopolymer was developed by using horse gram starch and corn starch. Diclofenac Sodium (DS) was used as the model drug to intercalate in to biopolymer matrix. Further, the compositions of the biopolymer matrix were optimized and the releasing of the model drug and the kinetics of the drug releasing was investigated.

METHODOLOGY

Preparation of novel biopolymer films

Solutions with various proportions of horse gram powder, corn starch, glycerol, 5% acetic acid were processed to form films by casting method. The homogenous

and clear slurry was prepared by dispersing starch and additives in distilled water. First 60 ml of distilled water was measured, and it was added into a 600 ml beaker. Then the measured amounts of starch were added into the beaker. Next 5 ml of glycerol was measured and was added in to the beaker. 5 ml of 5% acetic acid was measured and was added to the beaker and while gradually heating the contents up to 80 ± 5°C with stirring (600 rpm) and then kept for 8 min at 80 ± 5 °C.

Table 1: Compositions of selected biopolymers prepared for the TDDS study

Sample no	Horse gram particle size	Horse gram (wt.%)	Corn starch (wt.%)	Glycerol /(±0.05) ml	5% acetic acid /(±0.05)ml	Distilled water /(±0.05)ml
1	<63µm	100	00	5.00	5.00	60.00
2	<63µm	50	50	5.00	5.00	60.00
3	<63µm	25	75	5.00	5.00	60.00

Then the polymerized sample was transferred to 20 cm x 30 cm size Aluminium foil resting on a leveled surface for casting and then the films were dried in ambient temperature chamber at 25°C for 6 days. Three precisely defined compositions were selected for the preparation of drug loaded biopolymers. Compositions of selected biopolymers prepared for the TDDS study, are listed in Table1.

Intercalations of Drug

1% (w/w) of total weight amount of a selected model drug, Diclofenac Sodium (DS) was measured and was added to the mixture while it was stirring at 600 rpm speed at 80 ± 5°c temperature. The amount of drug, temperature and stirring speed used adjustable parameters.

Characterization of the drug loaded biopolymer

Then the drug loaded polymer samples were subjected to several laboratory tests and characterization techniques to determine the properties of the novel drug loaded polymer such as Functional group analysis using Fourier transform infrared spectroscopy (FTIR), Film morphology using Scanning Electron Microscopy (SEM), pH conditions, thickness, folding endurance, stickiness, transparency, water vapour Transmission Rate (WVTR), percentage moisture absorption, percentage moisture lost.

Preparation of the Phosphate Buffer Saline Solution (PBS)

Phosphate Buffered Saline (PBS Buffer) was used as the receptor solution for the diclofenac sodium under the *in vitro* skin permeation study [16-18]. First 8.00g of Nacl, 2.00 g of KCl, 1.44 g of Na_2HPO_4 and 0.24 g of KH_2PO_4 was added into

800ml of distilled water. Then it was mixed well, and pH of the resulting aqueous mixture was adjusted in to 7.4. Finally, total volume was adjusted up to 1L by adding distilled water.

Dialysis cell preparation

First 2.5cm x 5 cm size dialysis tube was taken, and one end was sealed using two 2.5 cm x 6cm glass plates and silicone glue. Then the resulting empty dialysis tube was soaked in 50 ml of PBS solution to open the tube. After 1 minute of soaking time tube was opened 2 cm x2 cm size polymer sample was placed inside, and PBS solution was adding to fill the empty space. Finally, the free end was tied up forming a dialysis cell (Figure 1).

Figure 1: Dialysis cell prepared for drug release study

In vitro release testing

In vitro release study was conducted with the aid of a Dialysis cell system (figure 1). The effective expose area of the drug loaded polymer section is 4.0 cm^2. Initially the donor compartment and the receiver compartment were filled with freshly prepared phosphate-buffered saline (PBS) solution of pH 7.4. The buffer solution in the receiver chamber was stirred with a magnetic stirrer at a speed of 80 rpm, to enhance homogeneous distribution of permeated drug in the receiver fluid. After the placement of the dialysis cell, 250 ml of PBS solution was placed in the receiver chamber and sealed with para- film to mitigate the environmental disturbances. Successful sink conditions were achieved by refilling the receptor solution after completely removing the already filled receptor solution with PBS solution in predefined periods of time. Therefore, 10 ml of the receptor solution was withdrawn continuously at predefined time intervals of 0.5 h (from 0.5 h to 8 h and after 24 h) and was used to quantify the drug concentration which was penetrated through the skin. All releasing studies were conducted at room temperature in triplicate. UV-Vis spectrophotometer (Evolution 201, thermo-scientific) was used to quantify the released drug under the wave length (276 nm) (Premarathne et al., 2016).

Releasing Kinetic studies

Release kinetics were determined by using five mathematical models such as Zero order, First order kinetics, Higuchi square root time model, Korsmeyer-Peppas Model, Weibull Model. By depending on the correlation factors (R^2) and the assumptions, drug releasing kinetics were comprehensively evaluated.

RESULTS AND DISCUSSION

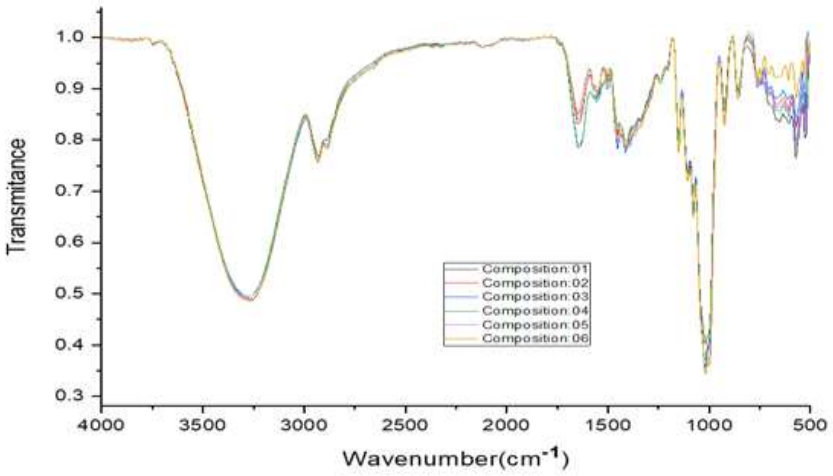

Figure 2: FTIR spectrum of all compositions

Figure 2 illustrate the FTIR spectrum of all the compositions which were included in the investigation. According to the FTIR spectrum, the characteristic peaks can be identified at 3287.51 cm^{-1} due to N-H stretching of secondary amine, at 1575.63 cm^{-1} regarding to C═O stretching of carboxyl ion, and 746.56 cm^{-1} respect to C–Cl stretching respect to Drug (DS).

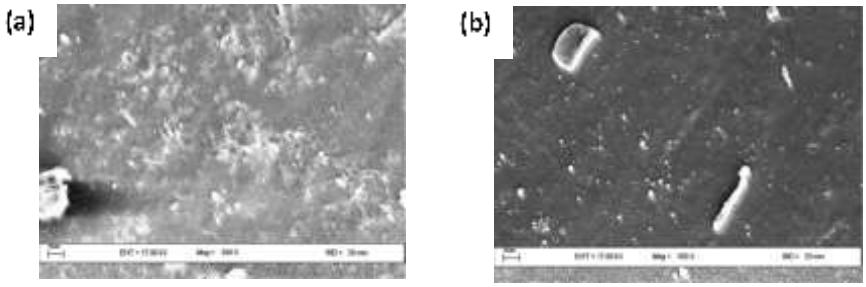

Figure 3: (a) SEM image for composition 1; **(b)** SEM image for composition 3.

SEM images clearly shows the surface morphology biopolymer before drug loading. All images show the porous texture of the polymer matrix. Below figure 3(a) and 3(b) shows the SEM images of best selected compositions (composition 1&3).

While the pH values obtained for the wet drug loaded polymers indicate pH values for the around 7.44. the results obtained from laboratory tests conducted to check parameters of the polymer are thickness, folding endurance, stickiness, transparency, WVTR, percentage moisture absorption and percentage moisture loss. Among those composition 3 shows minimum thickness, maximum folding endurance, maximum transparency, maximum and percentage moisture absorbance. Stickiness is minimum in composition 1while WVTR is high in composition 1. Percentage moisture loss is maximum in composition 2. But composition 3 shows considerably positive results for those tests as well. Hence composition 3 has been identified as the most promising sample.

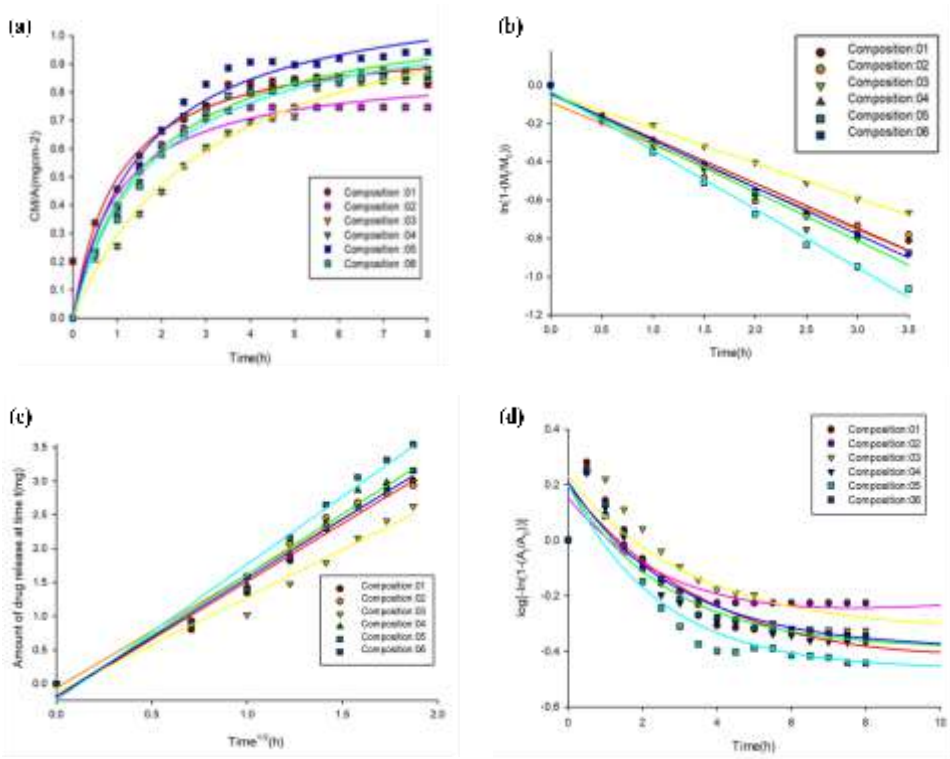

Figure 4: (a) Cumulative mass/Area vs time for all compositions; **(b)** First order kinetic model for first 3.5 hour of releasing of drug (t =0 to t = 3.5 h); **(c)** Higuchi square root time model for first 3.5 hour of releasing of drug (t =0 to t = 3.5 h); **(d)** Weibull model for first 8 hour of releasing of drug (t = 0 h to t = 8 h).

The Cumulative mass vs time plots for all compositions was illustrated in figure 4(a). It clearly shows that composition no 3 has a longer releasing time with respect to the other composition. Release Kinetics were studied, using the correlation coefficient (R^2) of the zero-order model, first-order model, Higuchi square root time model, Weibull method and Krosmeyer- Peppas model. In release kinetic studies (figure 4(b), 4(c), 4(d)), Diclofenac Sodium release mechanism shows an approach of a first order and Fickian controlled-diffusion model for 8 h. Further, due to biopolymer decay over time, the releasing of Diclofenac Sodium from the biopolymer matrix demonstrated two diffusion rates from t = 0 h to t = 3.5 h and t = 3.5 h to t = 8 h. As an overall result, the composition 1 and 3 can be identified as the best fit to this drug delivery system.

CONCLUSIONS/RECOMMENDATIONS

Among the selected three compositions (1, 2 & 3) to use in TDDS, composition 3 has shown promising potential. It also revealed that when the amount of corn starch increases, the ability to controlled release increases. In kinetic studies also, it has suggested that composition 3 has higher potential to serve as a drug delivery vehicle for control releasing of drug in pharmaceutical and cosmetic industries.

REFERENCES

1. Sonawane, A., Rajwade, Y., Singh, D., Desai, S., & Rajurkar, G. (2014). Moisture dependent physical properties of horse gram. *International Agricultural Engineering Journal*, *23*(2), 7-14. http://114.255.9.31/iaej/EN/Y2014/V23/I2/7
2. Panda, V., Suresh, S. (2015). Gastro-protective effects of the phenolic acids of Macrotyloma uniflorum (horse gram) on experimental gastric ulcer models in rats. *Food bioscience*, *12*, 34-46. https://doi.org/10.1016/j.fbio.2015.07.004
3. Kawsar, S. M. A., Huq, E., Nahar, N., & Ozeki, Y. (2010). Identification and quantification of phenolic acids in Macrotyloma uniflorum by reversed phase-HPLC. *American Journal of Plant Physiology*, *5*(4), 204-211. https://scialert.net/abstract/?doi=ajpp.2008.165.172
4. Premarathne, E. P. N., Karunaratne, D. N., & Perera, A. C. (2016). Controlled release of diclofenac sodium in glycolipid incorporated micro emulsions. *International Journal of Pharmaceutics, 29 Jul 2016, 511*(2), 890-898. https://doi.org/10.1016/j.ijpharm.2016.07.047

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