

Microstructured Adhesives for Modified Release of Transdermal Drug Delivery

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ABSTRACT

This study investigated the use of microstructured adhesives in transdermal patches. Microstructured 'foam' adhesives were fabricated and loaded with various model compounds. The characterization and performance properties of the microstructured adhesive systems are described.

INTRODUCTION

The field of microstructured (MS) adhesive is a new technology developed by 3M (1-2). This technology involves fabricating adhesives to make patterns of micro-wells that form discrete reservoirs or channels when overlain by a cap layer. The shape, size and distribution of the structures in the adhesive layer may be precisely controlled, allowing for a variety of advantages when used for transdermal delivery systems.

The structured PSA has potential advantages of enhanced drug loading capacity and options for separate compartmentalization of drug and excipients. This novel system may also provide modulating parameters for drug loading and releasing rates. The performance properties of the system can be designed by utilizing various types of microstructure-forming technologies such as open cell, closed cell, and multilayer.

EXPERIMENTAL METHODS:

Process to Fabricate Open Cell Adhesive Construction:

Microstructured adhesive materials were fabricated by embossing adhesive with a microstructured tool. In the present study, the microstructured tool was cut from polyimide to form a close-packed hexagonal pattern using laser ablation. The hexagonal posts were 125 microns tall, with a width of 115 microns wide at the top and 135 microns at the base, and a repeat distance of 175 microns. These dimensions create channels between the hexagonal posts that are 20 to 60 microns wide from bottom to top. The tool was treated with a release coating and uncured adhesive was extruded or coated onto the tool. A polyethylene terephthalate (PET) backing was laminated to the adhesive and the uncured adhesive was compressed to fill the channels in the tool. The adhesive was cured under UV lamps (GE-Black Light) with an energy of 1500 -1600 mJ/cm² for 5 - 20 minutes. Once the adhesive was cured and removed from the tool, it was characterized to determine the degree of replication. The height of the microstructured adhesive walls was determined using interferometry microscopy and wet-out against a glass substrate was determined using a light microscope.

PSA Formulations:

A hydrophobic adhesive formulation (A) was 90 parts isooctyl acrylate (IOA) and 10 parts acrylic acid (AA) by

weight. A hydrophilic adhesive formulation (B) was equal parts IOA, AA, and ethylene-10-monoacrylate by weight.

Drug Loading Methods:

Pre-polymerization drug loading involved directly dissolving or dispersing the medicinal ingredient in the adhesive monomer composition prior to polymerization.

Post-polymerization drug loading involved adding active substance dissolved in a solvent to a pre-formed PSA matrix. Suitable solvents include water, buffer, methanol, ethanol, isopropanol, and acetonitrile. 0.5% Propyl red (PR), methyl red (MR, Acros Co.), and tetracycline were loaded using this method. The resulting drug-loaded patches did not show any damage to the embossed microstructures. Also, some patches without release liner were immersed in 25% tetracycline hydrate-methanol solution for 10 seconds. After air-drying, the resulting patch showed a homogeneous dispersion of tetracycline throughout the adhesive matrix.

Single vs. Multi-laminated Adhesive Construction

Additional membrane layers, release liners, microstructured (MS) PSA, and/or non-structured PSA layers can be laminated to the adhesive construction to create encapsulated microscopic reservoirs within the laminate. The amount of void volume in the encapsulated reservoirs can be tailored by controlling the structures within each layer. Figures 1 and 2 show examples of multi-laminate constructions that may be used.

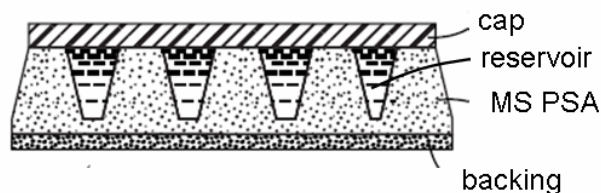


Figure 1. Non-structured (flat) PSA cap layer.

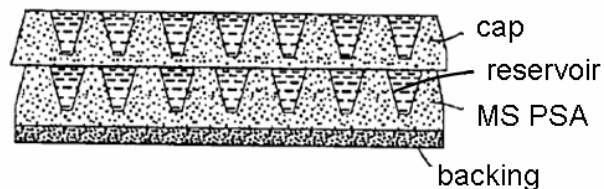


Figure 2. Microstructured PSA cap layer.

In Vitro Release Study

In vitro drug release studies were carried out by placing a 5 cm² patch in a drug release apparatus (Hanson SR8-Plus Dissolution Test System, Hanson Research Co.) equipped with a rotating basket. Each drug-loaded patch was brought into contact with 150 mL phosphate-buffered saline at 37°C. Samples were withdrawn at various times and analyzed by HPLC or spectrometric analysis.

RESULTS AND DISCUSSION

Characterization of Structured Adhesives:

Microstructured PSAs with honeycomb wells having 25 to 60 micron wide interconnected adhesive walls (Fig. 3) were made with the tool mentioned above. This pattern enables material to be entrapped. The height of the samples used in these experiments was typically 50 microns. Approximately 40% of the PSA wet-out when pressed against a glass plate, indicating that 60% of the planar surface area was void space (i.e. wells).

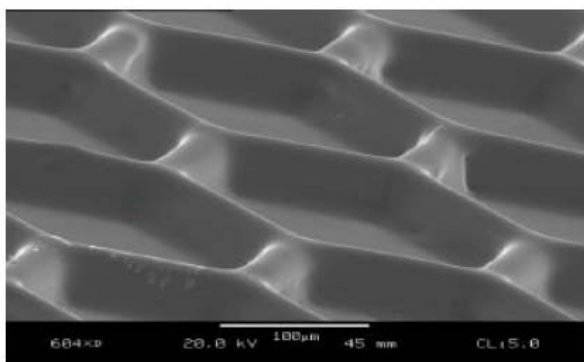


Figure 3. SEM of microstructured PSA with hexagonal pattern 90/10 IOA/AA, 50 micron deep, 200 micron pitch

To compare the effects of drug solubility, Propyl Red (PR) and Methyl Red (MR) were used as models for hydrophilic drugs and hydrophobic drugs, respectively.

The release profiles of MR and PR from the patches made of hydrophilic adhesive B are shown in Fig. 4. The release rate of MR was relatively fast - over 90% of the total amount within 24 hours. The results suggest that release of a small, hydrophilic compound from the patch was mainly influenced by solubility and diffusion rate. In case of the more hydrophobic PR, however, initial surface area of the patch governed the lag time and drug flux.

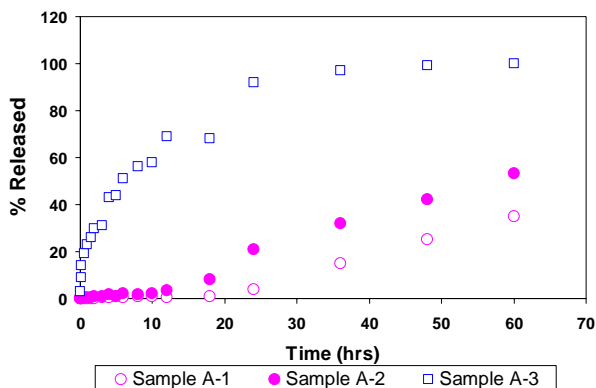


Figure 4. Cumulative release profiles of PR and MR from matrix dispersion-type system. Sample A-1: PR in flat adhesive; Sample A-2: PR in microstructured adhesive; Sample A-3: MR in microstructured adhesive.

Evaluation of Multi-laminated Adhesive Effect on Profiles of In Vitro Release:

Three multi-layer adhesive constructions and two single layer systems were loaded with tetracycline for drug release rate testing (shown in Fig. 5). Sample B-1 is a MS hydrophobic adhesive filled with tetracycline. Sample B-2 is a MS hydrophobic adhesive filled with tetracycline and capped with flat hydrophobic adhesive (as in Fig. 1). Sample B-3 is a MS hydrophobic adhesive filled with tetracycline and capped with MS hydrophilic adhesive (as in Fig. 2). B-4 is a MS hydrophobic adhesive filled with tetracycline and capped with flat hydrophilic adhesive. Sample B-5 is a flat hydrophobic adhesive without microstructures covered with tetracycline.

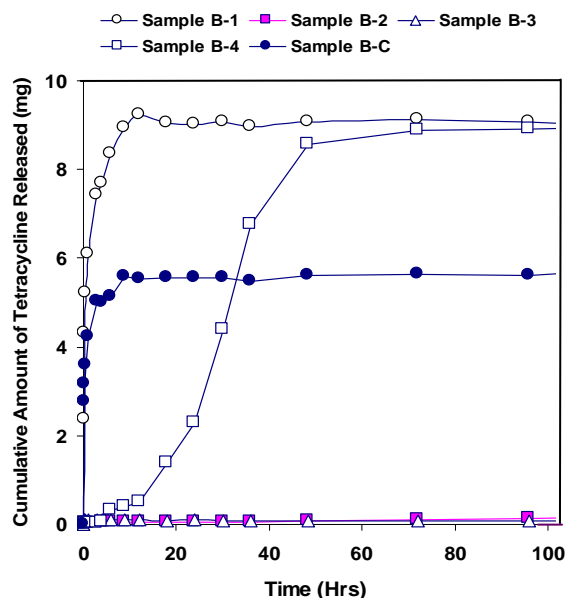


Figure 5. Cumulative release profiles of tetracycline from five different patch constructions

CONCLUSION

The ability to provide a defined void volume within a transdermal drug delivery system has a number of benefits and uses. Among these is the ability to contain a medicinal ingredient within the void volume, which can temporally alter the thermodynamic driving force in the skin contacting layer by replenishing the skin contacting layer with drug, penetration enhancers, or other excipients. The construction of the patch systems permits the drug to continuously replenish the skin contact layer as the drug is depleted during the wear period with a minimum of deformation of the device.

REFERENCES

1. Sher et al., U.S. Patent 6,197,397, 2001.
2. Mazurek et al., U.S. Patent 5,650,215, 1997.

ACKNOWLEDGEMENTS

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