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HSPiP, Computational Modeling, and QbD-Assisted Optimized Method Validation of 5-Fluorouracil for Transdermal Products

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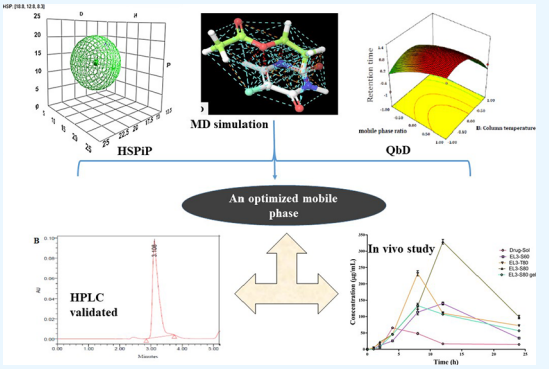
ABSTRACT: This study addressed the simplest and most efficient HPLC (high-performance liquid chromatography) method for the estimation of 5-fluorouracil (5-FU) from rat blood plasma by implementing the Hansen solubility parameters (HSP), computation prediction program, and QbD (quality by design) tool. The mobile phase selection was based on the HSP predictions and experimental data. The Taguchi model identified seven variables (preoptimization) to screen two factors (mobile phase ratio as A and column temperature as B) at three levels as input parameters in "CCD (central composite design)" optimization (retention time as Y_1 and peak area as Y_2). The stability study (freeze−thaw cycle and short- and long-term stability) was conducted in the rat plasma. Results showed that HSPiP-based HSP values and computational model-based predictions were well simulated with the experimental solubility data. Acetonitrile (ACN) was relatively suitable over methanol as evidenced by the experimental solubility value, HSP predicted parameters (δ_h of 5-FU − δ_h of ACN = 8.3−8.3 = 0 as high interactive solvent whereas δ_h of 5-FU − δ_h of methanol = 8.3−21.7 = −13.4), and instrumental conditions. CCD-based dependent variables (Y_1 and Y_2) exhibited the best fit of the model as evidenced by a high value of combined desirability (0.978). The most robust method was adopted at A = 96:4 and B = 40 °C to get earlier Y_1 and high Y_2 as evidenced by high desirability (D) = 0.978 (quadratic model with $p < 0.0023$). The estimated values of LLOD and LLOQ were found to be 0.11 and 0.36 μg/mL, respectively with an accuracy range of 94.4−98.7%. Thus, the adopted method was the most robust, reliable, and reproducible methodology for pharmacokinetic parameters after the transdermal application of formulations in the rat.



INTRODUCTION

Chromatographic techniques are applied to a quantity of pharmaceutical ingredients (PIs) in the blood plasma, urine, and skin tissue.[1] High-performance liquid chromatography (HPLC) is an advanced technique of chromatography applied in biological chemistry for identification and quantification of active compounds from biological samples (human plasma).[2,3] Moreover, high sensitivity and accuracy are the quality control parameters in HPLC method development as compared to conventional analytical techniques.[4] In order to understand the significance of delivering 5-fluorouracil (5-FU) in the skin, the quantification of the drug from biocomponents, the HPLC method was extensively developed, optimized, and validated to get reliable results for the analysis of 5-FU from human plasma and predicting various bioparameters of various drugs.[5−7]

Chemically, 5-FU is 5-fluoro-1,3-diazinane-2,4-dione extensively used in a variety of diseases, particularly in colorectal, breast, head, and neck. It is rapidly metabolized to produce cytotoxic fluoronucleotides with established anticancer effects.[8] Furthermore, 5-FU is a drug of choice clinically for skin cancer, vitiligo, and psoriasis.[9] It has a short plasma half-life (15−20 min), and a high dose is required for maintaining a therapeutic level in the blood.[10] Several analytical approaches have been reported for the quantification of 5-FU from the biological samples such as solid phase extraction (SPE), gas chromatography (GC), and LC−MS/MS.[11−13] These methods require highly sophisticated equipment and invasive methods (degraded in high temperature) that are expensive, tedious, time-consuming, and slow for routine clinical assay.[8] The reported techniques required a relatively large plasma volume (>2 mL) involving complex extraction procedures, low sensitivity, poor reproducibility, and high expenses, and

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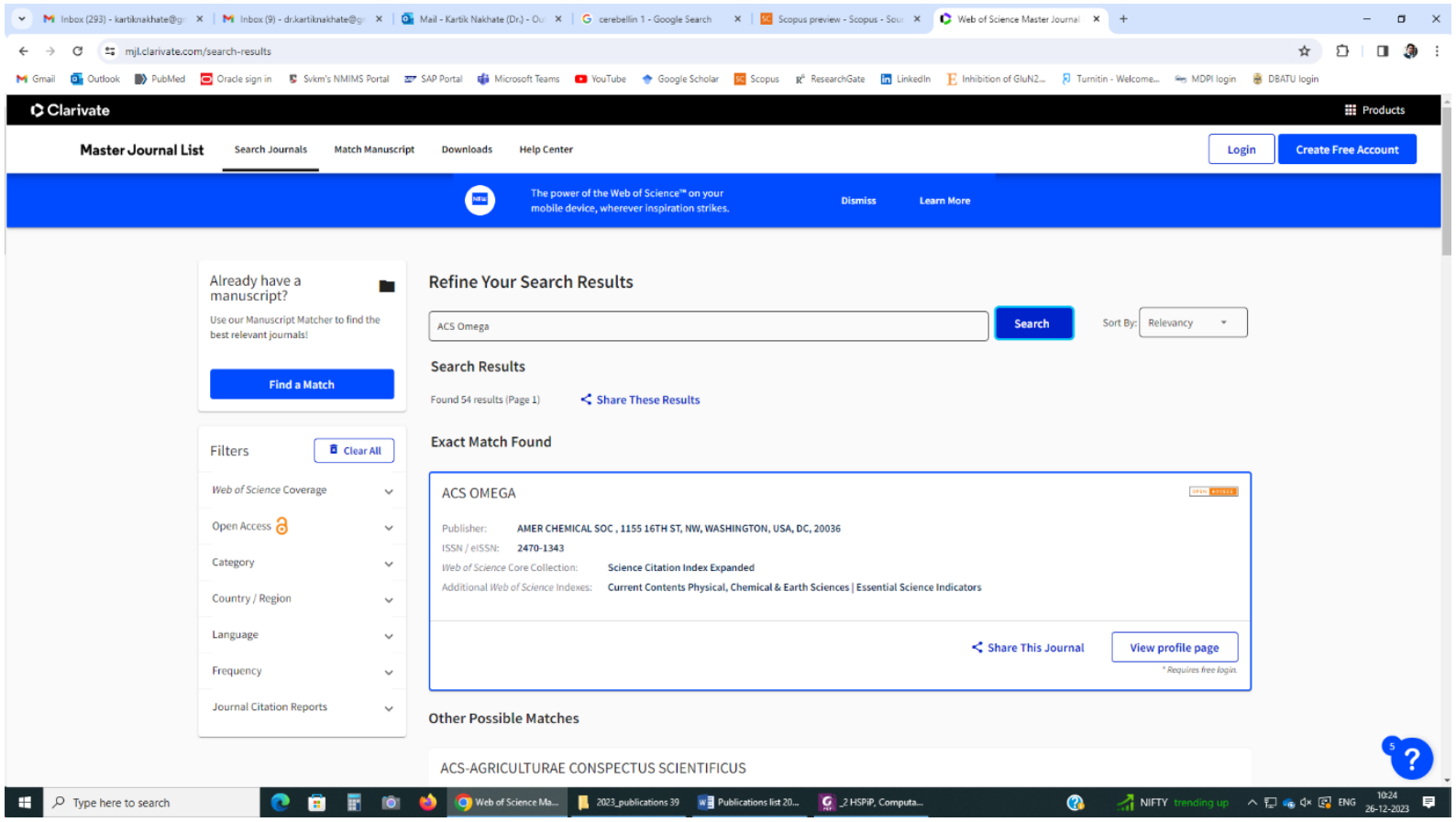
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