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Dissolution testing and potentiometric determination of famciclovir in pure, dosage forms and biological fluids

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ABSTRACT

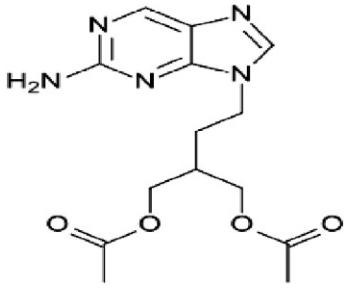
The performance characteristics of two new plastic membrane ion selective electrodes (ISEs) used for the determination of famciclovir (Fcv) based on the ion associate of Fcv with phosphotungstic acid (PTA) or phosphomolybdic acid (PMA) are described. Different experimental conditions as type of plasticizer to be incorporated in the membrane, life span, effect of soaking, pH, temperature, and interferences were studied. Both electrodes showed similar performance under these conditions, exhibiting Nernstian slopes of S (Fcv-PTA) = 58.60 ± 0.84 mV/decade and S (Fcv-PMA) = 58.77 ± 0.68 mV/decade within a usable concentration range of 10^{-5}–10^{-2} [Fcv/M] at 298/K. Famciclovir was assayed potentiometrically in its pure solution, pharmaceutical preparations and biological fluids (urine and plasma) using proposed electrodes under batch and flow injection analysis (FIA) conditions with a recovery % ranging between 96.76% and 102.83% having RSD of 0.66%–1.81%. The electrodes were also successfully applied in the determination of the dissolution profile of Fcv tablets and the results came in agreement with the validated results of the HPLC method obtained from the quality control unit of the company producing the tablets.

1. Introduction

Famciclovir (Fcv, Fig. 1), [as 2-[(acetyloxy) methyl]-4-(2-amino-9H-purin-9-yl) butyl acetate], is an oral prodrug which is converted by first-pass metabolism to the antiviral drug penciclovir [1]. Penciclovir (the active form of the drug), upon intracellular uptake, is monophosphorylated by virally-encoded thymidine kinase and, subsequently, converted to a triphosphate by cellular enzymes. Penciclovir triphosphate preferentially inhibits the DNA polymerase of susceptible viruses; at clinically relevant levels, there is no substantial effect upon cellular DNA polymerase, thereby minimizing side effects to the host [1]. It's used as an antiviral drug in the treatment of the Herpes viruses' infections, including herpes simplex 1 and 2 (cold sores and genital herpes) and varicella-zoster (shingles and chickenpox) [1].

(Scheme 1) Several analytical methods have been described for the determination of famciclovir in its pure state or in its pharmaceutical preparations including spectrophotometry [2–13], high performance liquid chromatography (HPLC) [14–18] and HPLC-mass spectrometry [19]. Recently, ISEs have been used in the pharmaceutical and biological analysis of many drugs [20–25]. Such electrodes are having wide linear range, fast in their response, non-destructive to the sample, not affected by color or turbidity, and very inexpensive so they are widely used [26].

In this work, two ion selective electrodes (ISEs) based on the formation of ion associate of famciclovir (Fcv) and phosphotungstic acid (PTA) or phosphomolybdic acid (PMA), in a plasticized PVC matrix, are introduced for the determination of famciclovir (Fcv) in its pure solution, pharmaceutical preparations and biological fluids (urine and plasma) under batch and flow injection analysis (FIA) conditions. The electrodes were successfully applied in monitoring the dissolution profile of famciclovir tablets.



Scheme 1. Structure formula of famciclovir.

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2. Experimental

2.1. Reagents and materials

All reagents used throughout the work were of analytical grade and solutions were made with doubly-distilled water. Pure grade famciclovir (Fcv) and pharmaceutical preparations: Propencivir® tablets (125 mg/tab) and (250 mg/tab) were provided by BIG (Bioriginal International Group, Egypt) under license from Novartis, Switzerland.

High relative molecular weight Polyvinyl chloride (PVC), Phosphotungstic acid (PTA) $H_3[P(W_3O_{10})_4.\ 24H_2O]$ and Phosphomolybdic acid (PMA) $H_3[P(Mo_3O_{10})_4].\ xH_2O$, and the placticizers: Dioctyl phthalate (DOP) $[C_{24}H_{38}O_4]$, Diethyl adipate (DEA) $[C_{10}H_{18}O_4]$, Diisononyl phthalate (DIP) $[C_{26}H_{42}O_4]$, Dibutyl sebacate (DBS) $[C_{18}H_{34}O_4]$, Dibutyl phthalate (DBP) $[C_{16}H_{22}O_4]$, Diethyl sebacate (DES) $[C_{14}H_{26}O_4]$ were purchased from FLUKA, Germany.

2.2. Apparatus

Laboratory potential measurements under batch conditions were carried out using a Jenway 3510 pH-meter (England). A Sentec packed saturated Calomel electrode (SCE) (England) was used as an external reference electrode.

The FIA system used in the analysis is depicted in Fig. 1. A one-channel flow system and a four-channel peristaltic pump (FIA lab 2500, Alitea, USA) equipped with PVC pump tubing from Rheodyne (Cotati, CA, USA) were used. The sample was manually injected using a six-port two position injection valve, with exchangeable sample loop of a well defined volume. The electrode was placed in a wall-jet cell and connected to a Jenway 3510 pH-meter (England) which has been interfaced to a strip chart recorder model BD111 from Kipp and Zonn (Deft, Netherlands). The ISE within the flow cup and the reference electrode were placed in a beaker where the level of the solution was kept 1 above the electrode surface.

2.3. Preparation of the electrode

The ion-exchangers, famciclovir phosphotungstate (Fcv-PTA) or famciclovir phosphomolybdate (Fcv-PMA), were prepared through the addition of 50 ml of 10^{-2} [Fcv]/M to 100 ml of 10^{-2} [PTA or PMA]/M of, respectively. The formed precipitates were washed by distilled water till chloride free (tested by $AgNO_3$ solution). Membranes of different compositions were prepared by mixing the required amounts of ion-exchangers, PVC and plasticizer (DOP, DEA, DIP, DBS, DBP or DES) (on testing effect of plasticizers) of total weight 0.35 g in a 7.5 cm (diameter) Petri-dish containing 10.0 ml tetrahydrofuran (THF) and 2.0 ml acetone [27].

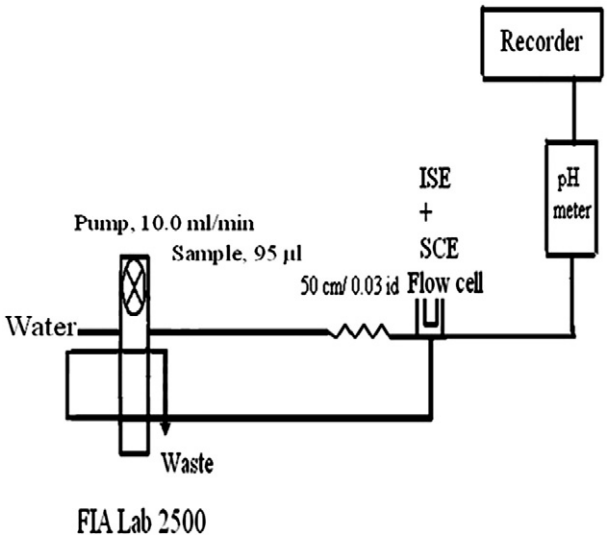

Fig. 1. Schematic diagram of the flow injection system used in measurements.

2.4. Construction of the calibration graphs

For batch measurements, the sensors were calibrated by being immersed in conjugation with the reference electrode in a series of standard Fcv solutions with concentration range 10^{-6}–10^{-2} [Fcv]/M. The values were plotted versus negative logarithmic value of the drug concentration (p drug).

For FIA measurements, a series of standard solutions of the drugs covering the range 10^{-5}–10^{-2} [Fcv]/M were injected to the flow stream and the corresponding peak heights were recorded and used to draw the calibration curves.

2.5. Potentiometric determination of the drug

The standard addition method has been used under batch conditions [28], where an incremental change is made by the addition of standard solution of 10^{-2} [Fcv]/M to the sample and recording the change in mV reading after each increment addition which has been used to interpret the concentration of the original sample.

For the analysis of tablets, the tablets were grinded, and then the appropriate weights of the drug were taken and dissolved in 100 ml to prepare a series of the drug ranging from 0.32 to 321.30 mg.

For the analysis of urine and plasma, different amounts of Fcv (0.32–321.30 mg) were taken and 5 ml of urine or 10 ml of plasma was added, then the volume was completed with distilled water to the mark in a 100 ml volumetric flask. In the case of plasma, pH was adjusted using 0.1 N NaOH and samples were placed in a refrigerator before their analysis using the standard addition technique as described above.

The peak height comparison method has been used under FIA conditions, where samples of different Fcv concentrations were injected into optimized FIA system, and then compared to those obtained from the injection of series standard solutions of the pure drug.

2.6. Dissolution testing

Tablet in situ dissolution measurements were made according to the guidelines mentioned in the USP monograph for famciclovir tablets using USP Type I, Erwika dissolution device, Germany, (USP-type apparatus). According to the authorized USP monograph of famciclovir, one tablet of either Propencivir® 125 mg or Propencivir® 250 mg was placed in a dissolution medium; 900 ml of 0.1 M HCl, which was maintained at 37.0 ± 0.5 °C, and the medium was agitated at a speed of 50 rpm. The reference electrode and the working electrode were dipped inside the apparatus vessel for the continuous recording of the potential [29]. The potential values were recorded until the potential reached the plateau then the dissolution profiles were constructed. To construct a calibration curve, which can be used for translating the measured potential into Fcv concentration and % dissolved, appropriate weights of the standard drug (50–300 mg) for Fcv-PTA and Fcv-PMA were added to 900 ml of the dissolution medium and the potential developed was plotted against the negative logarithmic value of the drug concentration (pdrug) [29].

3. Results and discussion

3.1. Effect of membrane composition under the batch conditions

As preliminary studies, PVC membranes plasticized with DOP plasticizer, with a ratio (1:1) and % composition containing 5.0, 7.0, 10.0 or