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DISCRIMINATION OF RELEASE KINETIC OF LOADED MICROBEADS DESIGNED FOR EMBOLISATION A NEW METHODOLOGY

F. Amyot[1], K. Jurski[1], V. Boudy[2], J.L. Counord[1], G. Guirfant[1], J. Dufaux[1], J.C. Chaumeil[2]

[1] Laboratoire de Biorhéologie et d'hydrodynamique Physico-chimique L.B.H.P. ESA C.N.R.S. 7057, 2 place Jussieu, 75251 Paris Cedex 05, France.

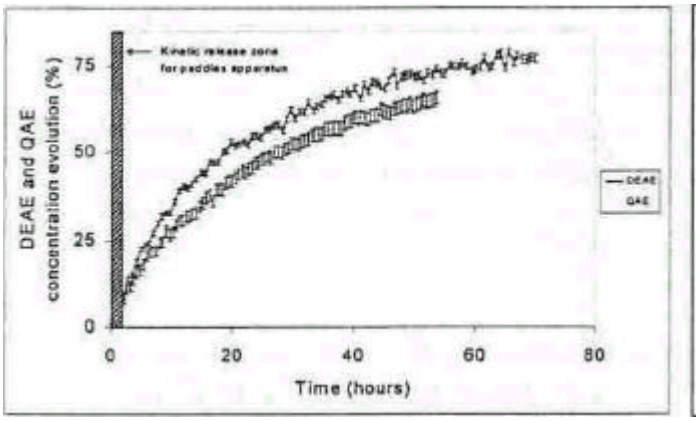
[2] Service Recherche et Développement Galénique, Pharmacie Centrale des Hôpitaux de Paris, Faculté des sciences pharmaceutiques et biologiques, 4 avenue de l'observatoire, 75270 Paris Cedex 06, France.

The development of a galenic form must take into account the drug physicochemical properties as well as the external conditions which govern its performances. In the case of loaded microbeads designed for embolisation. the drug release kinetic strongly depends on the local hydrodynamic conditions. Currently the apparatuses recommended by the European Pharmacopeia allow to measure *in vitro* these kinetics; but the measured kinetics are very different from those met in the *in* vho embolisation procedures.

The following paper presents a new methodology to evaluate the release kinetics of drugs from ion exchange resins. The methodology has been tested with a prototype which shows the feasibility of discriminating two closely related loaded galenical formulations. This study underlines experimentally and numerically the importance of the diffusive - convective transport mechanism on the drug release kinetic. This work is included in a project related to the local inflammation observed in the embolized zone. Consequently, the use of specific microbeads and drug is imposed, i.e. QAE Trisacryl LS and DEAE Trisacryl LS loaded with an anti-inflammatory (Indomethacin) [1], [2], [3] [4].

The installation consists of a duct connected to a one-closed-edge-tube with a length (L) to diameter (d) ratio high enough (L/d = 10) to provide diffusion and convection hydrodynamic conditions (Reynolds number Re = 860). This "T shape prototype" stands for a junction between an artery and an embolised vessel (named "cavity", which contains the loaded microbeads). The system was conceived to allow the visualisation of the physical phenomena encountered, to determine the residence time and the distribution of the released drug in both medium and cavity by UV absorption monitoring. The preliminary experimental results highlight the capability of the new device to achieve release kinetic measurements and to discriminate in the finest way two kinds of closely related microbeads (fig. 1). A numerical study is also presented to ensure the influence of the local dynamic conditions on the release kinetic [5], [6], [7] : at the upper part of the cavity, a convective zone is characterised by a three - dimensional successive eddies, with size and intensity clearly related to the flow conditions at the top of the cavity [8], [9]; at the down part of the cavity, a diffusive zone is achieved since the eddies tend to vanish progressively when reaching the bottom of the cavity. The drug concentration evolution clearly depends upon the hydrodynamic conditions in the cavity, i.e. the recirculating zone, which deforms the parallel drug iso-concentration lines (fig. 2). As mentioned previously, this main result indicates that the drug transport observed in *in vivo* embolisation procedures is firstly diffusive then convective dependent.

This numerical and experimental approach of the drug release shows clearly the fundamental influence of the hydrodynamic diffusive - convective interactions on the drug release rates from microbeads. This aspect is essential to obtain the discrimination of two closely related galenical formulations.



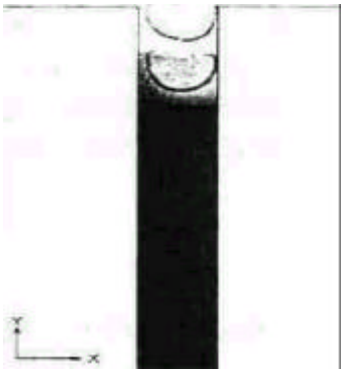


fig. I ; *Experimental release rates obtained with the « T » shape apparatus for DEAE ana QAE Trisacryl Indomethacin loaded microbeads, pointing out a discrimination between both loaded microbeads and a respective release half time ofl8h and 26h.*

fig. 2 : Numerical drug concentration evolution at the top of the cavity leading to the evidence of the influence of the recirculating zone on the distortion of the drug iso-concentration lines near the junction (concentration decreases from black to white colour).

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