and releasing highly hydrophobic drugs such as curcumin or celecoxib [3,4]. This derivative also showed long-circulating features after intravenous administration [4,5]. Based on these studies, we had the idea to load rifampicin into the INVITE nanomicelles and test these drug delivery systems for their activity against Mycobacterium smegmatis. which could be considered a good model, i.e., one that is less hazardous to manipulate with respect to Mycobacterium tuberculosis, to assess the antibacterial activity of our systems. As previously mentioned, INU was chemically-derived with VITE, and the obtained INVITE bioconjugate was allowed to form the nanomicelles, and loaded with the selected drug by the dialysis method. The drug-loaded micelles were lyophilized, and the gained powder was easily redispersed, allowing us to obtain a homogeneous dispersion in water or phosphate buffer of the insoluble drug. The calculated drug loading was 6% *w*/*w*. The antimicrobial activity of the rifampicin loaded micelles was determined with the macrodilution broth method, according to Clinical and Laboratory Standards Institute. The results returned an effective antibacterial activity, comparable to that of free rifampicin. This indicates that the drug does not show any loss in activity when included in INVITE nanomicelles, thereby showing that the developed drug delivery system is an important tool in a prospective use of it in the therapy of TB.

References: [1] Glaziou, P.; Sismanidis, C.; Floyd, K.; Raviglione, M. Global Epidemiology of Tuberculosis. *Cold Spring Harb. Perspect. Med.* **2015**, *5*, a017798. [2] Smith, T.; Wolff, K.A.; Nguyen, L. Molecular biology of drug resistance in Mycobacterium tuberculosis. *Curr. Top. Microbiol. Immunol.* **2013**, *374*, 53–80. [3] Mandracchia, D.; Trapani, A.; Perteghella, S.; Sorrenti, M.; Catenacci, L.; Torre, M.L.; Trapani, G.; Tripodo, G. pH-sensitive inulin-based nanomicelles for intestinal site-specific and controlled release of celecoxib. *Carbohydr. Polym.* **2018**, *181*, 570–578. [4] Tripodo, G.; Pasut, G.; Trapani, A.; Mero, A.; Lasorsa, F.M.; Chlapanidas, T.; Trapani, G.; Mandracchia, D. Inulin-D-α-tocopherol succinate (INVITE) nanomicelles as a platform for effective intravenous administration of curcumin. *Biomacromolecules* **2015**, *16*, 550–557. [5] Mandracchia, D.; Rosato, A.; Trapani, A.; Chlapanidas, T.; Montagner, I.M.; Perteghella, S.; di Franco, C.; Torre, M.L.; Trapani, G.; Tripodo, G. Design, synthesis and evaluation of biotin decorated inulin-based polymeric micelles as long-circulating nanocarriers for targeted drug delivery. *Nanomedicine* **2017**, *13*, 1245–1254.

3.5. Compounding of (Trans)Dermal Patches by Hot-Melt Ram Extrusion 3D Printing

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(Trans)dermal patches (TP) are well-known pharmaceutical preparations designed to provide prolonged drug delivery through the skin to achieve a local, regional or systemic effect. TPs are often preferred to other topically-applied dosage forms since they make it possible to predetermine the drug absorption kinetic and to define the treated area. Thus, TPs can reduce the side effects on healthy skin and due to an undesired systemic drug absorption when localized cutaneous diseases or injuries have to be treated. TPs are produced by a solvent casting technique, but they cannot be easily compounded since, after solvent evaporation, significant modifications of the adhesive matrix, and therefore, of the drug release and adhesive properties, can occur over an unknown period of time, ranging from some days to weeks. These alterations cannot be monitored in a pharmacy setting.

This work demonstrated the feasibility of the extemporaneous preparation of (trans)dermal patches by hot-melt ram extrusion 3D printing [1]. This technology makes it possible to easily define both the patch geometry and the dose according to patient needs. The TP preparation consists of three simple technological operations: (i) the drug, the film-forming material (Eudragit (Eu) RL, RS or blends thereof) and the plasticizer (triacetin, TRI, or try-butyl citrate, TBC), which confers the adhesive properties [2], are mixed in a mortar; (ii) the mixture is fed in to the chamber of the ram-extruder and heated to 90 °C; (iii) the melt mixture is printed with the desired geometry (thickness: 50 μm) on the backing layer and coupled with the release liner. The adhesive properties of printed patches were investigated by shear and 180°-peel adhesion tests. The results showed that patches with suitable adhesive properties can be printed using 40% *w*/*w* of TRI or 50% *w*/*w* of TBC. The TRI-containing patches showed higher shear adhesion values than TBC ones ($p < 0.05$). Since high values

of shear adhesion are essential for the patch permanence onto the skin, TRI (40% *w*/*w*) was selected to print drug-loaded patches, using 2.34% *w*/*w* of ketoprofen (KP) and 3% of nicotine (NT) as model compounds. Neither drug affected the patch adhesive properties, even if a reduction of shear adhesion up to 8-folds was observed based on the drug type and the EuRL/EuRS ratio. Finally, the in vitro release studies showed that the EuRL/EuRS ratio impacted significantly on the release rate of both the tested drugs. According to the well-known characteristics of the two copolymers, the higher the concentration of EuRL in the matrix, the higher the release rate of both KP and NT.

References: [1] Musazzi, U.M.; Selmin, F.; Ortenzi, M.A.; Mohammed, G.K.; Franzé, S.; Minghetti, P.; Cilurzo, F. Personalized orodispersible films by hot melt ram extrusion 3d printing. *Int. J. Pharm.* **2018**, *551*, 52–59. [2] Quaroni, G.M.G.; Gennari, C.G.M.; Cilurzo, F.; Guylaine, D.; Creton, C.; Minghetti, P. Tuning the rheological properties of an ammonium methacrylate copolymer for the design of adhesives suitable for transdermal patches. *Eur. J. Pharm. Sci.* **2018**, *111*, 238–246.

3.6. Preparation and Characterization of Water Soluble Carvacrol Prodrug-Clay Hybrids

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Pharmaceutical-grade clay minerals are widely used to encapsulate drugs, overcoming undesirable physicochemical properties or modifying the release kinetic of active compounds [1,2]. Among clay minerals, tubular Halloysite (HAL), stratified Montmorillonite (VHS), fibrous Sepiolite (SPT) and Palygorskite (PC) are largely used in the pharmaceutical field [3]. In our study, the prodrug approach was employed in the rational drug design of novel derivatives to improve carvacrol (CAR) solubility while still retaining the antibacterial activity. Preliminary results showed that WSCP1, WSCP2 and WSCP3 (CAR amino-acid esters) were the most active compounds against Gram positive bacteria, but were endowed with low plasma stability. The aim of this work was the adsorption of these three CAR derivatives on different clay minerals as a prior step to developing an adequate delivery system. Additionally, a complete characterization of the novel hybrids was conducted to elucidate the nature and degree of prodrug interactions with minerals clays. High performance liquid chromatography results and thermal analysis revealed that among the tested clay minerals, SPT and HAL retained lower amounts of the drug. Conversely, VHS followed by PC possessed the higher loading capacities, ranging from 20–25% for WSCP1- and WSCP3-VHS hybrids, 18–20% for WSCP1- and WSCP3-PC, and approximately 45% and 27% for WSCP2 loaded in VHS and PC. Considering the higher drug loading values, VHS hybrids were selected for further studies. X-Ray powder diffraction analysis confirmed the effective inclusion of prodrugs into the VHS interlayer by shifting of VHS basal spacing value. Fourier transform infrared spectra corroborated the interaction between the organic and inorganic components through the revelation of new bonds in the hybrid samples. Release studies carried out at pH 1.2 and 6.8 buffers revealed that the desorbed drug increased quickly in the first hour of the experiments until reaching a plateau phase in which the percentage of WSCPs in the buffer media remained constant for 8 h. After adsorption into VHS, a higher stability of WSCPs was achieved, especially at pH 6.8 phosphate buffer, thanks to the delayed release over time. In conclusion, adsorption of CAR derivatives onto pharmaceutical-grade clay minerals was successfully achieved, especially on VHS. In addition, WSCP stability in physiological conditions was improved due to the intercalation of WSCP1-3 into VHS interlayers, which protected the drugs from hydrolysis in the gastrointestinal simulated fluids.

References: [1] Aguzzi, C.; Cerezo, P.; Viseras, C.; Caramella, C. Use of clays as drug delivery systems: possibilities and limitations. *Appl. Clay Sci.* **2007**, *36*, 22–36. [2] Sandri, G.; Bonferoni, M.C.; Rossi, S.; Ferrari, F.;