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# Characterization, optimization, and development of an amorphous solid dispersion that generates amorphous nanoparticles during dissolution

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This research aimed to enable the repurposing of niclosamide as a viable pharmaceutical product for treating cancer and viral infections, including COVID-19. Niclosamide is an FDA-approved anthelmintic being studied in clinical trials as a chemotherapeutic and broad-spectrum antiviral. Additionally, several other applications are currently in the preclinical stage. Unfortunately, niclosamide is a poorly water-soluble molecule with reduced oral bioavailability, which hinders its use for new indications. Moreover, niclosamide is a poor glass former; in other words, the molecule tends to recrystallize, and it is virtually impossible to generate a stable amorphous solid employing the neat molecule. To overcome these challenges, we developed an amorphous solid dispersion (ASD) of niclosamide using hot-melt extrusion (HME). Unexpectedly, this ASD generated nanoparticles during its dissolution, increasing niclosamide's apparent solubility by more than 60-fold (i.e. from 6.6 ± 0.4 to 481.7 ± 22.2 µg/mL). The ASD material was characterized using differential scanning calorimetry (DSC), X-ray diffraction (XRD), nuclear magnetic resonance (NMR), and Fourier-transform infrared (FTIR). The nanoparticles were observed by dynamic light scattering (DLS), and their properties were confirmed by cryogenic transmission electron microscopy (cryo-TEM) and Wide-angle X-ray scattering (WAXS). The nanoparticles are amorphous, with a mean particle size of about 100 nm. These amorphous nanoparticles act as drug reservoirs, increasing drug diffusion, as determined in vitro by using side-by-side diffusion cells. These in vitro tests were translated to a rat model that also showed increased oral bioavailability in Sprague–Dawley rats.

Nevertheless, niclosamide ASD undergoes recrystallization in acidic media, and an enteric oral dosage form was needed for its translation into the clinic. Initially, niclosamide ASD was formulated using commercial enteric capsules and as enteric-coated tablets. The enteric dosage forms were tested using pH-shift dissolution and acid-uptake tests, using the USP type II dissolution apparatus and the disintegration apparatus, respectively. The capsules exhibited a higher weight gain percentage and visual rupture. In contrast, enteric-coated tablets protected the formulation from acid ingress and maintained the performance of niclosamide ASD granules during dissolution. These enteric-coated tablets were administered to beagle dogs at a niclosamide dose of 75 mg/kg, resulting in plasma concentrations of niclosamide higher than those reported in the literature using solubilized niclosamide at a higher dose (i.e., 100 mg/kg).

In summary, an enteric oral dosage form of niclosamide ASD was formulated without hindering

the generation of nanoparticles while maintaining the increase in the niclosamide's apparent solubility.

References

[1] Jara, M.O. et al. (2023), doi.org/10.1016/j.jddst.2023.104187.
[2] Jara, M.O. et al. (2022), doi.org/10.3390/pharmaceutics14122568.
[3] Jara, M.O. et al. (2021), doi.org/10.1016/j.ijpharm.2021.120701.
[4] Jara, M.O. et al. (2021), doi.org/10.3390/pharmaceutics13010097