Rhein methotrexate-decorated solid lipid nanoparticles altering adjuvant arthritis progression

Wessam M. El-Refaie[1], Mostafa S. Ghazy[1], Fady A. Ateyya[1], Eman Sheta[2], Mohanad Y. Shafek[1], Mahmoud S. Ibrahim[1], Mahmoud M. Ahmed[1], Mennatallah A. Gowayed[1]

[1]Departments of Pharmaceutics & Pharmacology, Faculty of Pharmacy, Pharos University in Alexandria, Alexandria, Egypt
[2]Department of Pathology, Faculty of Medicine, Alexandria University, Alexandria, Egypt

Introduction

Methotrexate (MTX) and Diacerein (DIA) are two of the most potent Disease-Modifying Anti-Rheumatic Drugs used for the treatment of Rheumatoid arthritis (RA). DIA has reflected some GIT and hepatobiliary manifestations in numerous cases. It undergoes biotransformation in the liver into the active metabolite Rhein (RH) which is characterized by its excellent anti-inflammatory activity and lower side effects. However, the hydrophobic nature of RH together with its low bioavailability does not encourage its use in RA. The current study aims to use RH in combination with MTX in targeted Solid Lipid Nanoparticles (MTX-RH-SLNs) for better effectiveness and lower adverse effects.

Materials and Methods

MTX-RH-SLNs were prepared using the high shear homogenization method and assessed for their quality attributes including particle size, zeta potential, entrapment efficiency, and structural properties using transmission electron microscopy.

The effect of the formulation was assessed in-vivo in adjuvant arthritis (AA) animal model.

Experimental Groups:

I. Non-arthritic healthy control rats (NC)
II. AA rats -oral dose of the vehicle
III. AA rats -methotrexate (MTX, 1 mg/kg/week; i.p.)
IV. AA rats -oral dose of Rhein solution (RH; 10 mg/kg)
V. AA rats -oral dose of MTX and RH solution (MTX 150 μg/kg -RH10 mg/kg)
VI. AA rats -oral dose of MTX in solid lipid nanoparticles (MTX-SLNs; 150 μ g/kg).
VII. AA rats -oral dose of RH in solid lipid nanoparticles (RH-SLNs; 10 mg/kg).
VIII. AA rats -oral dose of MTX and RH in solid lipid nanoparticles (MTX-RH-SLNs)

Tested drugs were administered for 15 days, from day 14 to the end of the study (day 28 from adjuvant injection).

Results

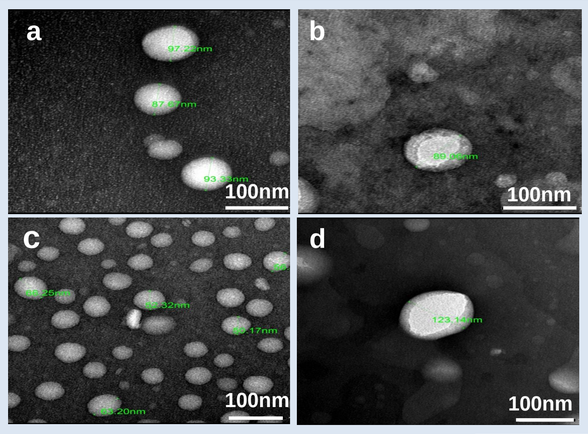

Fig. 1: TEM micrographs of the prepared SLN.

a) Drug free SLN
b) MTX-SLN
c) RH-SLN
d) RH-MTX SLN

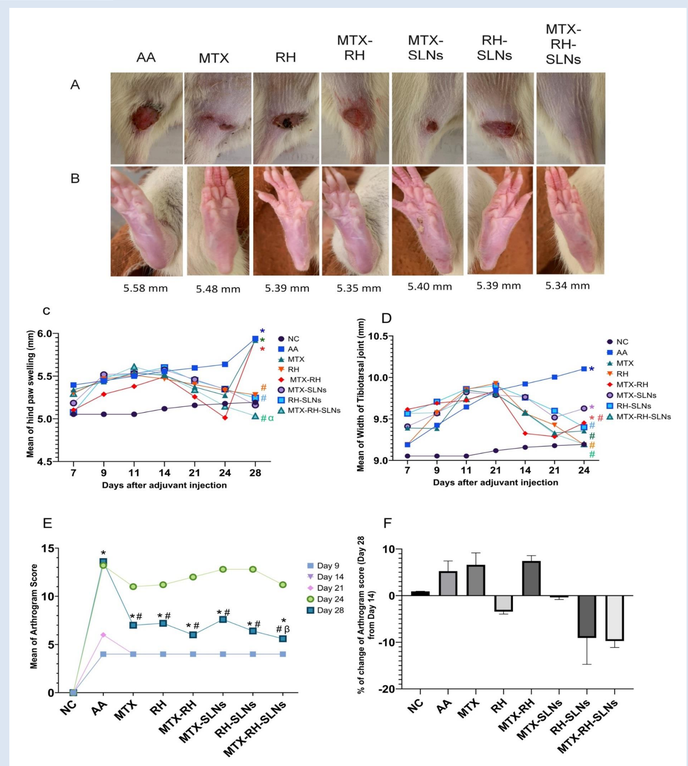

Fig. 2: Hind paw swelling and Arthrogram score.

* compared to NC,
# compared to AA,
δ compared to MTX,
α compared to MTX-RH,
β compared to MTX-SLNs,
χ compared to RH-SLNs;
$p<0.05$ (n=8)

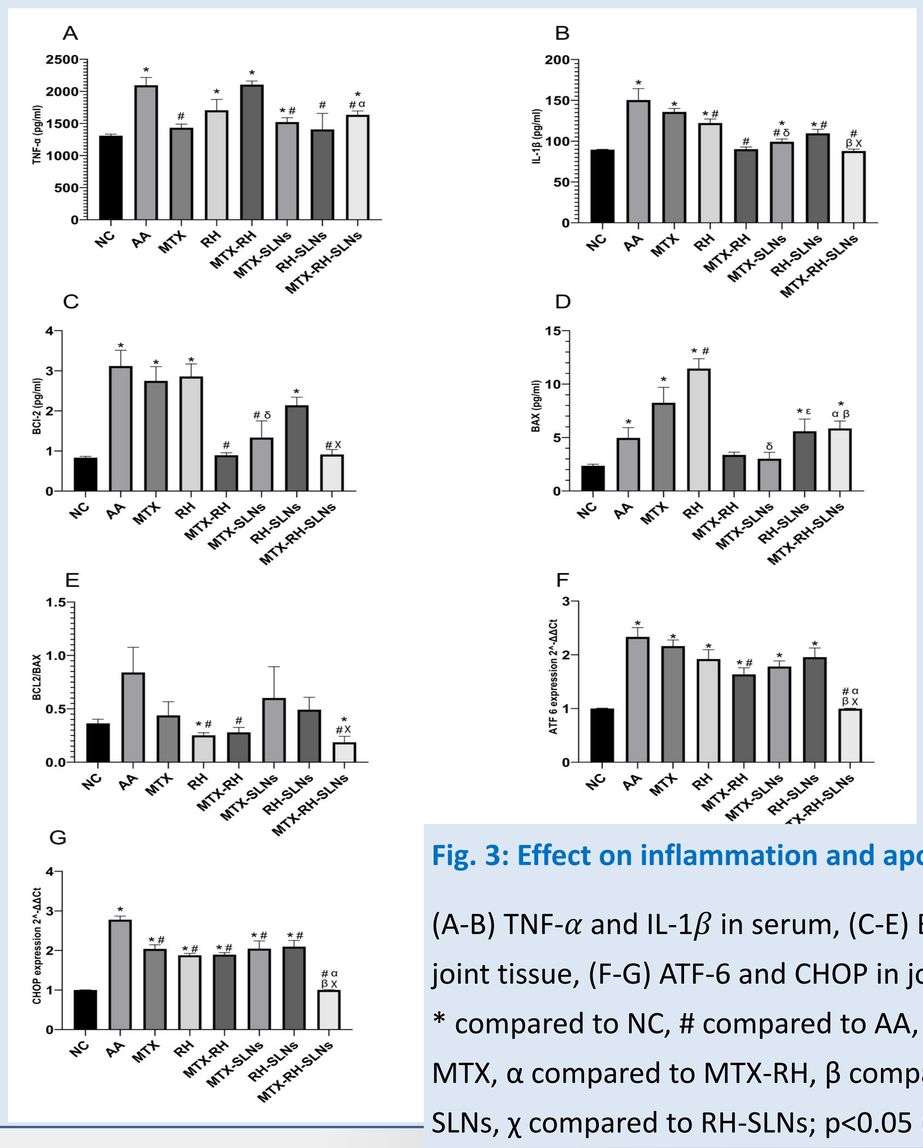

Fig. 3: Effect on inflammation and apoptosis.

(A-B) TNF-α and IL-1β in serum, (C-E) BCl-2 and BAX in joint tissue, (F-G) ATF-6 and CHOP in joint tissue;
* compared to NC, # compared to AA, δ compared to MTX, α compared to MTX-RH, β compared to MTX-SLNs, χ compared to RH-SLNs; $p<0.05$ (n=8)

Conclusions

Results revealed that MTX-RH-SLNs were in the suitable nanosize range with high negative zeta potential indicating good stability. In-vivo, MTX-RH-SLNs significantly improved all measured inflammatory and arthritic markers, confirmed by electron microscopy, immunohistochemistry, and histology examination of the joints. In conclusion, MTX-RH-SLNs can represent a promising therapeutic approach for RA.

References

1. Jain A, Mishra SK, Vuddanda PR, Singh SK, Singh R, Singh S. Targeting of diacerein loaded lipid nanoparticles to intra-articular cartilage using chondroitin sulfate as homing carrier for treatment of osteoarthritis in rats. Nanomedicine Nanotechnology, Biol Med. 2014;10(5):e1031-e1040. doi:10.1016/j.nano.2014.01.008
2. Emam AA, Ali NW. Validated determination of diacerein and its active metabolite, rhein, by stability indicating constant pattern method as a novel manipulation of zero order spectra. Bull Fac Pharmacy, Cairo Univ. 2018;56(1):73-79. doi:10.1016/j.bfopcu.2017.11.005
3. Wang Y, Liu Z, Li T, et al. Enhanced therapeutic effect of RGD-modified polymeric micelles loaded with low-dose methotrexate and nimesulide on rheumatoid arthritis. Theranostics. 2019;9(3):708-720. doi:10.7150/thno.30418
4. Louthrenoo W, Nilganuwong S, Nanagara R, Siripaitoon B, Collaud Basset S. Diacerein for the treatment of rheumatoid arthritis in patients with inadequate response to methotrexate: a pilot randomized, double-blind, placebo-controlled add-on trial. Clinical rheumatology. 2019;38(9):2461-71.
5. Pavelka K, Bruyere O, Cooper C, Kanis JA, Leeb BF, Maheu E, et al. Diacerein: benefits, risks and place in the management of osteoarthritis. An opinion-based report from the ESCEO. Drugs & aging. 2016;33(2):75-85.
6. Feng H, Zhu Y, Fu Z, Li D. Preparation, characterization, and in vivo study of rhein solid lipid nanoparticles for oral delivery. Chemical Biology & Drug Design. 2017;90(5):867-72
7. Gowayed MA, El Achy S, Kamel MA, El-Tahan RA. Polymyxin B prevents the development of adjuvant arthritis via modulation of TLR/Cox-2 signaling pathway. Life Sciences. 2020;259:118250