METRONIDAZOLE NANO POLYMERS: PREPARATION, CHARACTERIZATIONS AND RELEASE STUDY

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The administration of drugs designed to be given as a single dose rather than multiple doses has recently been made possible using extended release formulation approach; the release of the drugs can be accomplished over long periods of time, enabling an almost constant level of the drug to be maintained in the bloodstream. Moreover, extended release formulations increase the clinical efficacy of drugs. The introduction of drug nanocomposites as extended release vehicles has provided a breakthrough in novel drug delivery systems in the field of pharmaceutical technology, for which nanopolymers are widely used for this purpose. This study aimed to achieve the preparation of new extended release formulation of metronidazole (MET) via loading of the MET onto nanopolymers in order to increase the residence time in the body by extended release.

Three nanocomposites were prepared using chitosan (CSNPs), alginate (AlgNPs) and chitosan-alginate (CS-AlgNPs) nanoparticles; MET-CSNPs, MET-AlgNPs and MET-CS-AlgNPs nanocomposites, respectively. The prepared nanocomposites were studied for their physiochemical properties, loading efficiency (LE), encapsulation efficiency (EE), and release.

The MET-CSNPs nanocomposites were prepared by mixing different concentrations of CS (0.5, 1, and 2 mg/mL) with TPP solutions (0.5, 1, 2.5 mg/mL) under controlled pH at 4.5 using NaOH. The product was centrifuged at 10000 rpm for 15 min and dried. The same procedure was repeated for the preparation of MET-CSNPs nanocomposites using different concentrations of MET (100, 200, and 400 mg).

The MET-AlgNPs were prepared by ionic gelation method between sodium alginate (1, 2 and 4 mg/mL) and cross-linking agent of $CaCl_2$ (0.5, 0.75, and 1% w/v) in the presence of MET (100, 200, and 400 mg).

MET-CS-AlgNPs nanocomposites were prepared using solutions of CS (0.5, 1 and 2 mg/mL), sodium alginate (2 and 4 mg/mL) and $CaCl_2$ (0.5 and 1%) at 100 mg MET concentration.

XRD spectra of MET-CSNPs showed two peaks at $2\theta=12^o$ and 23.7^o, indicating amorphous forms due to cross-linkage with TPP. XRD spectra of MET-AlgNPs showed three diffraction peaks at 2θ values 14.1^o, 21.8^o and 39.1^o. XRD patterns of MET-CS-AlgNPs showed overlap between patterns of CS and Alg, which lead to the appearance of peaks at $2\theta = 14.5^o$ and 20.6^o.

The FTIR data for all nanocomposites prepared in this work showed the spectra of nanopolymers (CSNPs, AlgNPs and CS-AlgNPs) as well as the spectra of MET. This result indicates the incorporation of MET in the nanopolymers.

Correlation and multiple regression analyses were used in this work to examine the relationship between dependant variables (EE, LE, particle size and zeta potential) and independent variables

(concentrations of CS, TPP and MET) for all nanocomposites. At MET-CSNPs nanocomposites, the MET concentration had a significant effect on the EE, LE and particle size. The TPP concentration significantly affected the particle size and zeta potential. In addition, CS concentration only affected the LE and zeta potential.

In the case of MET-AlgNPs nanocomposites, the MET concentration only had a significant effect on the zeta potential. In addition, the variable $CaCl_2$ had a significant effect on the LE only. On the other hand, the Alg concentrations affected all dependant variables significantly except the zeta potential.

In regards to the MET-CS-AlgNPs nanocomposites, the independent variables were Alg, $CaCl_2$ and CS concentrations. The Alg concentrations significantly affected all dependant variables except EE. In addition, the $CaCl_2$ concentrations significantly affected all dependant variables except LE, whereas the CS concentrations significantly affected the EE and particle size.

Extended release study of MET from its respective nanocomposites was carried out using 0.1N HCl and showed that the release rate of MET from the MET-CSNPs nanocomposites was slower than MET-AlgNPs and MET-CS-AlgNPs. These results indicate extended release of the drug from its respective nanocomposites, and therefore these nanocomposites have good potential to be used as extended-release formulation of the drugs.

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LIST OF ABBREVIATIONS OR SYMBOLS

MET	Metronidazole
CSNPs	Chitosan nanoparticles
AlgNPs	Alginate nanoparticles
CS-AlgNPs	Chitosan-Alginate nanoparticles
MET-CSNPs	Metronidazole-Chitosan nanoparticles
MET-AlgNPs	Metronidazole-Alginate nanoparticles
MET-CS-AlgNPs	Metronidazole-Chitosan-Alginate nanoparticles
CS	Chitosan
Alg	Sodium alginate
LE	Loading efficiency
EE	Encapsulation Efficiency
HPLC	High-performance liquid chromatography
TPP	Tri-Poly-Phosphate
NaOH	Sodium hydroxide
$CaCl_2$	Calcium Chloride
XRD	X-ray diffraction
FTIR	Fourier-transform infrared spectroscopy
PBS	Phosphate Buffered Saline
UV-Vis	Ultraviolet–visible spectroscopy
DLS	Dynamic light scattering
BSA	Bovine serum albumin
PDI	Polydispersity index
R	Correlation of coefficient
R^2	Coefficient of determination
SPSS	Statistical Package for the Social Sciences