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Formulation Design and Functional Characterisation of a Novel Vaginal Mucosal Drug Delivery System

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SUMMARY

The aim of this research was the development, characterisation, and optimisation of composite polymer-based formulations for vaginal drug delivery using metronidazole (MTz) as a model drug to treat bacterial infection in the vagina. Blank (BLK) composite wafers comprising carrageenan (CARR) and sodium alginate (SA) were initially formulated and tested. However, due to poor physico-chemical properties, further formulations were developed involving combination of carbopol (CARB) with SA or CARB with CARR, modified with hydroxypropylmethyl cellulose (HPMC) in different weight ratios and plasticised with polyethylene glycol (PEG 200). Drug loaded (DL) wafers were obtained by loading selected optimised composite CARB-CARR or CARR-SA based gels with 0.75% of MTz prior to freeze-drying. Formulations were characterised using texture analyser (hardness, mucoadhesion), scanning electron microscopy (SEM), X-ray diffractometry (XRD), swelling capacity and *in vitro* drug dissolution study using HPLC.

INTRODUCTION

Vaginal drug delivery systems have become common and successful in today's market and are still undergoing development as the future lies in developing novel bioadhesive systems (tablets, liposomes, noisome and microparticles) for achieving fully controlled drug delivery at the mucosal site (Bassi & Kaur, 2015). Mucoadhesive polymer-based systems have been introduced to avoid hepatic first pass effect, prolong duration of drug in the vagina and avoid messiness and leakage. Various marketed products comprise bioadhesive polymers with ideal properties such as low production costs, avoidance of organic solvents and ease of self-administration with no need to use applicators (Acarturk, 2009).

MATERIALS AND METHODS

Lyophilised wafers were prepared by freeze-drying gels combining different ratios of low/high molecular weight SA and CARR with CARB, with or without HPMC or PEG. Blank formulations were functionally characterised for their mechanical strength (hardness), adhesion, porosity (%), swelling capacity, SEM and XRD to select the optimised formulation for MTz loading. The DL wafers (0.75% MTz) were further characterised as above in addition to drug content (assay) and dissolution (release) profiles using HPLC (Ahmed et al., 2018). All tests were done in triplicates (N = 3).

RESULTS AND DISCUSSION

The combination of CARB and CARR and CARR and SA at optimum concentrations, showed an improved cone shaped structure and smooth surfaces (compared to wafers based only on SA or CARR) for easy vaginal insertion, porosity and mechanical properties which were then selected for drug loading. The optimum BLK formulations based on hardness profiles were, 6% CARB:CARR 1:3 + 1% HPMC, 6% CARB:CARR 1:1 + 1% HPMC, 8% CARB:

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SA 1:9, 8% CARB:SA 1:2 + 8% PEG200 and 8% CARB:SA 1:4, as they showed values between the ideal ranges of 5-8 N (Fig 1). According to Fig. 1, lower concentration of CARB in composite BLK wafers improved their hardness profiles. The adhesion results showed low peak adhesive force (PAF) and total work of adhesion (TWA) but high cohesiveness values.

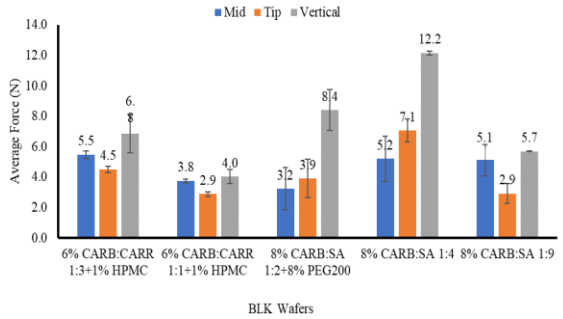


***Fig. 1**. Mechanical properties of BLK wafers. Each data point is the mean ±SD (N = 3).*

Most of the formulations showed relatively low swelling capacity below 400% and disintegrated within 3-4 hrs except for 8% CARB: SA 1:9 wafer which achieved the highest swelling capacity and lasted until 72 hrs before disintegrating (Fig 2). DL 8% CARB:SA 1:9 wafers also showed high swelling capacity of 698 ± 67% over 72 hrs which will be ideal for prolonged drug release.

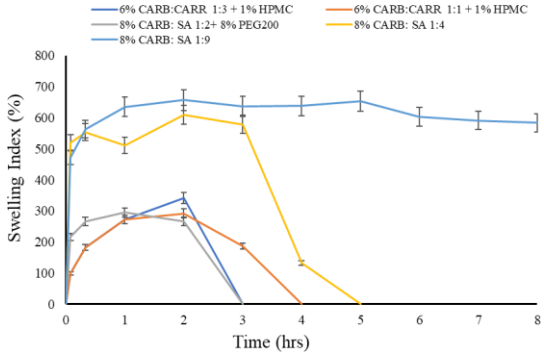
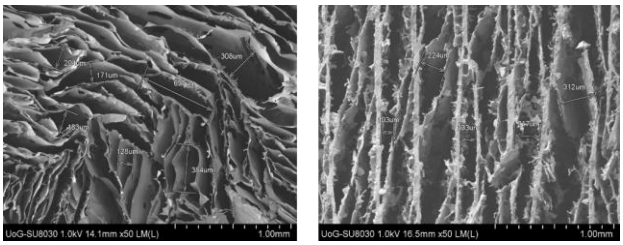


***Fig. 2.** Swelling profiles of BLK wafers. Each data point is the mean ± SD (N = 3).*

The SEM results showed porous internal morphology with the MTz loaded wafers showing a more compacted structure with dispersed drug crystals on the pore walls (Fig 3). The MTz loaded CARB:CARR wafers had lower % porosity than CARB:SA wafers except DL 6% CARB:CARR 1:1 + 1% HPMC.

XRD showed amorphous nature for the BLK wafers, while the DL wafers showed crystalline peaks attributed to MTz (confirmed by SEM).



BLK *DL*

***Fig. 3.** SEM micrographs showing the internal porous structure and surface morphology of BLK and DL wafers*

However, crystallinity was lower compared to the pure MTz, which is advantageous in terms of better swelling of the wafer matrix. Based on the hardness profiles of DL formulations, 8% CARB:SA 1:4 + 0.75% MTz and 8% CARB:SA 1:9 + 0.75% MTz wafers were chosen for *in vitro* drug dissolution studies. The release profiles were almost linear for both formulations and lasted until 72 hrs which shows potential for prolonged release of the drug upon insertion. The drug dissolution data followed Higuchi model, and they achieved almost 100% release over 72 hrs.

CONCLUSION AND FUTURE WORK

Low CARB content improved hardness profiles and all DL wafers showed low PAF and TWA but high cohesiveness. DL 8% CARB:SA 1:9 wafer showed high hydration capacity which will be ideal for prolonged drug release. The wafers were porous and amorphous in nature with crystalline peaks in DL wafers attributed to MTz. Future work will involve biological characterisation including antimicrobial, biocompatibility (MTT assay), bioadhesion and irritation tests and comparison with other commercial vaginal delivery systems. A major challenge is insertion without damaging the wafers, therefore a suitable applicator will need to be designed.

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