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Aspirin Loaded Xerogels for Buccal and Oral Delivery for Patients with Dysphagia to Target Deep Vein Thrombosis

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SUMMARY

This study aimed to develop xerogels for delivery of aspirin via the oral (buccal mucosa and GIT) route in geriatric patients with dysphagia. Xerogels were prepared using low molecular weight chitosan (CS), carrageenan (CAR) and metolose (MET) in different ratios, loaded with aspirin (75 mg). Gels (2.5% w/v and 4.0% w/v) were prepared (60 °C) using 40% v/v ethanol and freeze dried for 48 hours. Xerogels (2.5% w/v MET: CAR 3:1 and 1:1, 4.0% CAR: CS 1:3 and 1:1 and 4.0% MET: CS 1:3 gels) were characterised with texture analysis (TA) for hardness and mucoadhesion, swelling index (%) and porosity (%) to identify an optimised formulation for controlled release (buccal) and fast release (GIT) delivery. Scanning electron microscopy (SEM) was used to assess surface morphology and X-ray diffraction (XRD) to assess the physical form of the formulations (amorphous or crystalline). Xerogels from 2.5 % w/v MET: CAR 3:1 and 1:1 gels showed higher swelling capacity (%) (more than 2 hours to disintegrate) and can be applied to the buccal mucosa for controlled delivery of the API while 4.0 % w/v CAR: CS 1:3 and 1:1 can be used as rapid release xerogel (disintegrated within 2 minutes) for oral GIT delivery.

INTRODUCTION

Deep vein thrombosis (DVT) results from a blood clot or thrombus expanding in the large veins of the legs or pelvic area (Vascular Disease Foundation, 2012). Demographic ageing, which is expected to cover 30% of the EU population by 2050 is likely to be of major significance in the coming decades. This will require more prescribed medicines due to the presence of new diseases and they are also more vulnerable to dysphagia due to natural process of aging, which can make swallowing of medicines challenging. Therefore, alternative solutions specifically tailored to the special needs of older populations are required by enhancing the development of novel delivery systems to improve safety, efficacy and patient compliance and increasing the product patent life cycle (Panda, 2012). Fast dissolving and sustained release lyophilised xerogels are examples of innovative formulations for buccal mucosa and oral GIT delivery. Composite lyophilised xerogels comprised of metolose (MET), carrageenan (CAR) and low molecular weight chitosan (CS) loaded with 75 mg of aspirin have been developed for potential oral (GIT and buccal mucosa) delivery.

MATERIALS AND METHODS

Different composite xerogels were formulated by freeze-drying process. Composite gels were prepared

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by combining MET with CAR (MET: CAR), MET with CS (MET: CS) and CAR with CS (CAR: CS) in different weight ratios (Table 1). Functional characterisation tests [mechanical hardness, in vitro mucoadhesion, swelling capacity (in phosphate buffered saline – PBS, and simulated saliva – SS, at pH of 6.8) and porosity (%)] were performed in order to select the optimised aspirin loaded xerogel for further advanced analytical characterization (scanning electron microscopy (SEM), x-ray diffraction (XRD), differential scanning calorimetry (DSC) and subsequent selection of optimised formulations for eventual oral GIT and buccal mucosa delivery.

RESULTS AND DISCUSSION

The composite xerogels obtained from 2.5% w/v MET: CAR 1:1, 3:1 and 4.0% w/v MET: CS 3:1 and 4.0% CAR: CS 1:1, 3:1 gels were elegant in appearance and non-brittle in nature proving to be suitable for potential GIT and buccal mucosa delivery respectively. For the formulations composed of 2.5% w/v MET: CAR 1:1 and 3:1, the hardness increased significantly ($p < 0.05$), whilst the swelling capacity (%) and mucoadhesion decreased with increase in MET content (Table 1). Hydration results from Table 1 showed that % swelling capacity was higher in PBS than in SS due to differences in ionic strength of the media (Peh, 1999). The hardness results showed that xerogels with higher resistance to compression were less able to swell due to collapsed pores, while the adhesion decreased due to reduced interaction. The xerogels comprising 4.0% CAR: CS 1:1 and 3:1 showed similar profile as the 2.5% MET: CAR 1:1 and 3:1, however, the hardness increased significantly ($p< 0.05$) with increased CS content with resultant decrease in the swelling capacity (%) and increase in the mucoadhesion profile. Table 1 shows that as the concentration of MET and CS increased, the formulation swelled less due to higher hardness. The stickiness (distance travelled before detachment from the model mucosa surface) of 2.5% w/v MET: CAR 1:1 and 3:1 formulations were significantly different with a value of 2.31 mm and 1.40 mm respectively, showing that increased concentration of MET decreased the stickiness (cohesiveness) of the formulations (Figure 1). For the 4.0% CAR: CS 1:1 and 3:1, the stickiness slightly increased from 0.76 mm to 0.86 mm respectively, with increased CS. SEM showed a porous internal morphology as a result of ice nucleation formed during freeze-drying and XRD showed that the drug loaded xerogels were crystalline in nature due to aspirin. Based on these results, the formulations from Table 1, can be tested further for drug release to find the optimised xerogel for buccal and oral GIT delivery systems respectively.

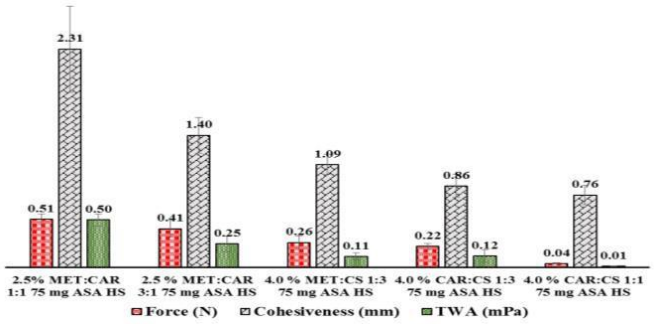

Fig. 1. *Mucoadhesion of aspirin loaded xerogels in human saliva.*

Table 1. *Physicomechanical characteristics of aspirin (ASA) loaded xerogels*

Formulations	Hardness (N)	Porosity (%)	Swelling capacity (%) SS	Swelling capacity (%) PBS
2.5% MET: CAR 3:1 75 mg ASA	5.19 ± 0.03	82 ± 12	302 ± 52	313 ± 21
2.5% MET: CAR 1:1 75 mg ASA	1.58 ± 0.14	71 ± 2	527 ± 69	540 ± 40
4.0% MET: CS 1:3 75 mg ASA	2.62 ± 1.08	75 ± 7	179 ± 35	201 ± 37
4.0% CAR: CS 1:3 75 mg ASA	4.46 ± 0.47	58 ± 7	134 ± 11	154 ± 10
4.0% CAR: CS 1:1 75 mg ASA	1.10 ± 0.10	69 ± 9	164 ± 10	215 ± 23

CONCLUSIONS

Lyophilised 2.5% w/v MET: CAR 1:1 and 3:1, 4.0% w/v CAR: CS 1:1 and 3:1 as well as 4.0% MET: CS 1:3 seems to be very promising systems for the administration of low dose aspirin for older patients with dysphagia and other age-related problems.

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