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1   **Formulation, characterisation and stabilization of buccal films for**

2   **paediatric drug delivery of omeprazole**

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30 **Abstract**

31 This study aimed to develop films for potential delivery of omeprazole (OME) via the buccal

32 mucosa of paediatric patients. Films were prepared using hydroxypropylmethylcellulose

33 (HPMC), methylcellulose (MC), sodium alginate (SA), carrageenan (CA) and metolose

34 (MET) with polyethylene glycol (PEG 400) as plasticiser, OME (model drug) and L-arg

35 (stabilizer). Gels (1% w/w) were prepared at 40°**C** using water and ethanol with PEG 400 (0 -

36 1% w/w) and dried in an oven (40°**C**). Optimised formulations containing OME and L-arg

37 (1:1, 1:2 and 1:3) were prepared to investigate the stabilization of the drug. Tensile properties

38 (Texture analysis - TA), physical form (differential scanning calorimetry – DSC; X-ray

39 diffraction – XRD; thermogravimetric analysis - TGA) and surface topography (scanning

40 electron microscopy SEM) were investigated. Based on the TA results, SA and MET films

41 were chosen for OME loading and stabilisation studies as they showed a good balance

42 between flexibility and toughness. Plasticised MET films were uniform and smooth whilst

43 unplasticised films demonstrated rough lumpy surfaces. SA films prepared from aqueous gels

44 showed some lumps on the surface, whereas SA films prepared from ethanolic gels were

45 smooth and uniform. Drug loaded gels showed that OME was unstable and therefore required

46 addition of L-arg. The DSC and XRPD suggested molecular dispersion of drug within the

47 polymeric matrix. Plasticised (0.5 % w/w PEG 400) MET films prepared from ethanolic

48 (20% v/v) gels and containing OME: L-arg 1:2 showed the most ideal characteristics

49 (transparency, ease of peeling and flexibility) and was selected for further investigation.

50

51 **Keywords:** Buccal drug delivery, Plasticiser, Oral films, Omeprazole, Paediatric

Introduction

Amongst all the established routes of drug administration, the oral route is perhaps the most preferred for both patients and healthcare providers compared to other routes such as injections. However, this route of administration has disadvantages including enzyme degradation within the gastrointestinal tract which prohibits oral administration of certain classes of drugs such as peptides and proteins. Evidence has shown that the oral mucosa is relatively permeable with a rich supply of blood and shows a short recovery time after stress or damage. Further, it also lacks Langerhans cells which allow the oral cavity to be tolerant of any potential allergens (1). Drug administration within the oral mucosa is generally classified into sublingual and buccal delivery. Among all the trans-mucosal routes, the buccal mucosa has excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa, hence suitable for the administration of retentive dosage forms (2-3). Direct access to the systemic circulation through the internal jugular vein bypasses hepatic first pass metabolism leading to relatively high bioavailability compared to the GI tract. Additionally, the buccal mucosa has a high surface area (50.2 cm^2) and a thin membrane (500–600 μm) which can contribute to rapid and extensive drug absorption (4).

Oral drug delivery systems have always been an important means of drug administration; however, many paediatric patients resist solid dosage forms such as tablets due to the bitter taste and fear of choking. Though sweetened liquid formulations are commonly used, they present many challenges including bitter after taste, unpleasant flavours, short half lives once opened and generally bulky to handle and store. Oral thin films offer easy administration and handling, rapid disintegration and dissolution, bypass first-pass metabolism, enhanced stability and taste masking for bitter drugs, local and systematic drug delivery, rapid onset of action and no trained or professional person is required for paediatric administration (5). Due to the numerous advantages of buccal dosage forms, various technologies have been explored to manufacture oral films on a large scale as an alternative to traditional dosage forms such as tablets and capsules (6).

Numerous buccal delivery systems in the form of tablets, liquids and semi-solids have been reported in the past decades yet only a limited number of these have reached the market (7). The necessity of recurrent dosing might possibly arise due to the flushing activity of saliva, chewing and the ingestion of food materials which results in the rapid expulsion of drugs. Moreover, the drugs in the saliva may be unevenly distributed, which might consequently

86 lead to lower amounts being absorbed by the mucosal tissues directly into the systemic
87 circulation. Furthermore, the likely displacement of the formulation from the buccal area by
88 tongue movements serves as an additional challenge (8). The above notwithstanding, the
89 buccal mucosal route is still considered a practical route to deliver a variety of active
90 ingredients.

91

92 Hydrophilic polymers incorporating several hydrogen bonding groups make the formulation
93 of bioadhesive buccal formulations feasible. Modified forms of such hydrogel polymers with
94 better bioadhesivity create second-generation mucosal dosage forms (9). In the present study
95 we report on the development of solvent cast films for buccal delivery in paediatric patients
96 using various hydrogel polymers generally regarded as safe (GRAS) and used in mucosal
97 formulations (10-13) including HPMC, MC, CA, MET, SA, plasticiser (PEG 400), OME
98 (model drug) and L-arg (to stabilise OME). Various parameters such as drying times and
99 temperatures, casting solvents as well as polymer and plasticiser concentrations were
100 investigated and the films subsequently characterised as part of the development and
101 optimisation.

102

103 **Methods**

104 *Materials*

105

106 Carrageenan (CA) and sodium alginate (SA) were gifts from FMC Bio-Polymer and
107 originally sourced from Cork (Republic of Ireland). Metolose (MET) was obtained from Shin
108 Etsu (Stevenage, Hertfordshire). Hydroxypropylmethylcellulose (HPMC), methylcellulose
109 (MC), polyethylene glycol (PEG 400), L-arginine (L-arg) were obtained from Sigma-Aldrich
110 (Gillingham, UK). Ethanol was purchased from Fisher Scientific (Loughborough, UK).
111 Omeprazole (OME) obtained from TCI (Tokyo, Japan).

112

113 *Formulation (gel and film) development*

114 Aqueous and ethanolic gels of the different polymers were prepared prior to film casting.

115 The aqueous gels were formulated by adding the required weight of polymers to the relevant

116 solvent (deionised water) at laboratory temperature ($22°C$) to obtain 1% w/w gels. Following

117 complete hydration (dissolution), the polymeric gels were heated to $40°C$. Based on the total

118 weight of polymers, various amounts of the plasticiser (PEG) were added to obtain different

119 concentrations (0.00%, 0.10%, 0.25%, 0.50%, 0.75% and 1.00% w/w) in the final gels

120   prepared. The resultant gels were left on a water bath with regulated temperature of 40°C

121   (except for CAR which was prepared at 70°C) and stirring continued for 30 min to achieve a

122   homogeneous dispersion. For ethanolic gels, the appropriate volume of ethanol (10% and

123   20% v/v) was added to yield the 1% w/w total concentration. The solution was left to cool to

124   room temperature and stirred again for 30 min. The final solutions were left to stand

125   overnight to remove entrapped air bubbles. After removal of the air bubbles, 20 g of each gel

126   was poured into Petri dishes (86 mm diameter) and kept in a pre-heated oven at 60°C for 24

127   h. The dried films were then carefully peeled off from the Petri dish, images captured using a

128   digital camera and transferred into poly bags and placed in a desiccator over silica gel at

129   room temperature until required.

130

131   *Formulation development and optimization of OME loaded films*

132   The main purpose for the development and optimization was to determine the optimised

133   amount of the drug that could be incorporated into the solvent cast film whilst still

134   maintaining the ideal physical characteristics in terms of flexibility, homogeneity and

135   transparency (14). The OME-loaded films were obtained by initially preparing MET gels as

136   previously described above. However, the drug was added to the appropriate volume of water

137   / ethanol to form an OME solution as can be shown in table 1. The polymer was then added

138   slowly to the vigorously stirred drug solution at room temperature to obtain the drug loaded

139   gels. The resulting gels were covered with parafilm as above, and left overnight to allow air

140   bubbles to escape, and then 20 g was poured into Petri dishes and dried at 40°**C** (15).

141

142   Table 1- Drug loaded MET gels formulated using different solvent systems and containing

143   different amounts of PEG 400 (0 and 0.5% w/w).

Solvent Systems	Water: ethanol(ml)	MET (g)	OME (g)	Plasticizers (g)	
				0%	0.5%
Water	50:0 (1:0)	0.50	0.10	0.00	0.25
10% v/v ethanol	45:5 (9:1)	0.50	0.10	0.00	0.25
20% v/v ethanol	40:10 (4:1)	0.50	0.10	0.00	0.25

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Stabilization of OME in drug loaded MET films using L-arg

Due to the breakdown of OME following gel formation, L-arg was used as a stabilising agent to prevent drug degradation. Table 2 shows the details for the different ratios of OME and L-arg in the gel formulations which were investigated. This step was performed by using different amounts of L-arg within the gel whilst keeping the original OME concentration (0.10% w/w) constant. The gels were prepared as above with L-arg and OME dissolved in the solvent before addition of MET and PEG 400.

Table 2 – Different OME: L-arg ratios in the MET gel formulations for preparing both unplasticised and plasticised films (0 and 0.5% w/w (PEG 400 respectively)

Solvent Systems	Water: ethanol (ml)	MET (g)	Drug (g) OME	OME : L-arg (g)			Plasticizers (g)	
				1:1	1:2	1:3	0%	50%
Water	50:0 (1:0)	0.50	0.10	0.10	0.20	0.30	0.00	0.25
10% *v/v* ethanol	45:5 (9:1)	0.50	0.10	0.10	0.20	0.30	0.00	0.25
20% *v/v* ethanol	40:10 (4:1)	0.50	0.10	0.10	0.20	0.30	0.00	0.25

Characterization of the films

Tensile characterisation by texture analysis

Texture analysis (TA) was used to measure tensile properties. A texture analyser (HD plus, Stable Micro System, Surrey, UK) equipped with 5 kg load cell was used. Thickness and width of the films were measured and stress and strain values were calculated based on these values. Data evaluation was performed by texture exponent-32 software program. The films free from any physical defects, with the average thickness of (0.07 ± 0.01 mm) were selected for testing. The films were cut into dumb-bell shaped strips and fixed between two tensile grips positioned 30 mm apart and stretched at a test speed of 1.0 mm/s to break point. The tensile strength (brittleness of the film), elastic modulus (rigidity) and percentage elongation (flexibility and elasticity) were determined using equations 1, 2 and 3. Each testing was carried out in triplicate (n = 3)

$$\text{Tensile strength} = \frac{\text{Force at failure}}{\text{cross-sectional area of the film}} \qquad (1)$$

$$\text{Percent elongation at break} = \frac{\text{Increase in length at break}}{\text{Initial film length}} \times 100 \quad (2)$$

$$\text{Young's modulus} = \frac{\text{slope of stres-strain curve}}{\text{Film thickness} \times \text{Cross head speed}} \qquad (3)$$

Scanning electron microscopy (SEM)

SEM was used to investigate the surface morphology of the films and to check for film uniformity and the presence of any cracks. The films were analysed using a Hitachi Triple detector CFE-SEM SU8030, (Roland Schmidt, Hitachi High-Technologies Europe GmbH) scanning electron microscope**.** Films were mounted onto 12 mm aluminium pin stubs (G301, Agar Scientific) with double-sided adhesive carbon tapes (G3347N, Agar scientific) and chrome coated (Sputter Coater S150B, 15 nm thickness). The coated films were analysed at 2 kV accelerating voltage.

Differential scanning calorimetry (DSC)

DSC was used to characterise the thermal behaviour of selected optimised MET and SA films and pure materials to investigate changes in their properties with introduction of PEG and drug within the films. Analysis of the films and starting materials were carried out on a Q2000 (TA Instruments) calorimeter. About 2.5 mg of each sample was placed into hermetically sealed Tzero aluminium pans with a pin hole in the lid and heated from -40°C to 180°C at a heating rate of 10°C/min under constant purge of nitrogen (100 ml/min).

Thermogravimetric analysis (TGA)

TGA studies were performed using a Q5000 (TA instrument) thermogravimetric analyser. About 2.5 mg of sample (films and starting materials - MET and SA) was placed into hermetically sealed Tzero aluminium pans with a pin hole in the lid. Samples were heated under nitrogen atmosphere at a flow rate of 25 ml/min from ambient temperature to 600°C at a heating rate of 2°C/min.

X-ray diffraction (XRD)

202 XRD was used to investigate the physical form (crystalline or amorphous) of the selected

203 optimised films and starting materials (MET, SA and PEG). XRD patterns of films and

204 starting materials were obtained with a DIFFRAC plus instrument (Bruker Coventry, UK)

205 equipped with an XRD commander programme. A Goebel mirror was used as mono-

206 chromator which produced a focused monochromatic $CuK\alpha_{1\&2}$ primary beam (λ=1.54184 Å)

207 with exit slits of 0.6 mm and a Lynx eye detector for performing the experiment. The

208 operating conditions during the experiment were 40 kV and 40 mA. Film samples were

209 prepared by cutting into 2 cm^2 square strips, mounted on the sample cell and scanned between

210 2 theta of 0° to 70° and counting time of 0.1 second step size.

211

212 **Results and Discussion**

213

214 *Formulation development and optimisation*

215 Omeprazole is an ideal candidate for buccal drug delivery using polymeric films as the

216 delivery system, as it degrades readily in acidic medium and undergoes first pass metabolism

217 (16). The polymers used in this study were chosen because of their hydrophilic nature.

218 Stirring was applied during gel formulation to prevent formation of lumps which could occur

219 through incomplete hydration especially for polymers with high viscosity. The heat (40°**C** or

220 70°C) reduced the viscosity of the final gels and helped to facilitate the escape of entrapped

221 air bubbles caused by stirring and also allowed ease of pouring into the casting Petri dishes.

222 Ethanol was used as solvent in addition to deionised water because some polymers/ drugs are

223 more soluble in ethanol than water and the former also helped to increase the rate of drying.

224 The removal of the air bubbles entrapped inside the gel was essential to avoid any empty

225 gaps, which could lead to non-uniform distribution of various film components. The drying

226 process for unplasticised gels was shorter (12 h) compared to plasticised gels (18-24 h) due to

227 the known water affinity of most plasticisers (17).

228

229 *Visual evaluation of films*

230 The MET and SA films were transparent, uniform and easy to peel from the Petri dishes.

231 However, though HPMC, MC and CA films were transparent, they were not uniform due to

232 the presence of air bubbles during drying, and were difficult to peel off without damaging the

233 films (figure 1). Further, HPMC and MC films showed excessive elasticity at high

234 concentrations of PEG which made them sticky. As a result, films prepared using CAR,

235 HPMC and MC was discontinued from further investigations and only MET and SA films
236 were taken forward for further development and drug loading.

237

238 Further development of MET and SA films, during the preliminary experiments, involved
239 preparing films with and without plasticiser. The main purpose of using plasticiser is to
240 provide flexibility and to overcome the brittleness in films. Un-plasticised MET and SA films
241 were brittle whilst films plasticised with PEG showed reduced brittleness and desirable
242 flexibility (18). Optimum plasticiser concentration(s) for further formulation development
243 was however, investigated by using texture analysis to determine film tensile properties
244 which provided more reliable data for accurate evaluation.

245

246 *Tensile properties of films*
247 Generally, soft and weak polymers have low tensile strength, low elastic (Young's) modulus
248 and low percent elongation at break. On the other hand soft and strong polymers display
249 acceptable strength, low elastic modulus and high percent elongation at break (17). The films
250 showed significant differences in the tensile strength (brittleness) based on the PEG
251 concentration. The initial linear portion of the stress-strain curve was used to estimate the
252 elastic modulus and tensile strength (19). The effects of PEG concentration on the tensile
253 strength values of the MET and SA films are shown in figure 2a and 2b respectively. The
254 percent elongation at break point of MET gradually increased with increased concentration of
255 PEG. It has been suggested that the average percent elongation at break point should ideally
256 be between 30-60% (17) which indicates a good balance between flexibility and elasticity.
257 MET films prepared from gels containing 0.5 and 0.75 % w/w of PEG satisfied these criteria.
258 MET films prepared from aqueous and ethanolic (water, 10% v/v and 20% v/v of EtOH) gels
259 containing 0.50% w/w PEG, showed % elongation of break values between 27-57%.
260 Unplasticised films prepared using water as the casting solvent showed a very low percent
261 elongation at break (figure 2 a) whilst films obtained from EtOH (10% v/v and 20% v/v) gels
262 showed a showed significantly higher values of percent elongation. There was also a general
263 increase in percent elongation with increasing concentration of PEG for all films. At the
264 concentration of 0.75% w/w of PEG, all the films showed elongation at break point of 55-
265 58% which was deemed high. Compared to MET films, SA films demonstrated low values in
266 the overall % in elongation break.
267 Generally, plasticisers such as PEG in the system increase the free volume between the
268 polymeric chains and allow them to slide past each other and subsequently produced

9

269 appropriate flexibility and consequent decrease in tensile strength and elastic modulus (20).

270 Based on these observations all subsequent gels for drug loading were prepared using only

271 MET at two concentrations (0.00 % and 0.50 % w/w (original gel) of PEG, with the

272 unplasticised films being used as a control.

273

274 *Physical evaluation of drug loaded films*

275 When OME is added to water, it dissolves quickly to produce a clear solution. After adding

276 polymer and desired amount of plasticiser in solution for gel formation, the stability of OME

277 plays a vital role in the overall stability of the gel (21). However, it was observed that OME

278 degraded within 20 minutes and changed the colour of the gel to red as can be seen in figure

279 3a. This resulted in a completely opaque and brown coloured film as shown in figure 3b.

280 OME can only be stable in alkaline solution with pH of 8 and stability can be achieved in two

281 main ways: (i) introducing cyclo-dextrin or (ii) L-arg to the drug loaded gel. However,

282 because of the toxicity of cyclo-dextrin for paediatric patients, use of L-arg was the preferred

283 option (22). To determine the optimum concentration of L-arg required to stabilize the drug

284 and determine its effect on MET film properties, different amounts relative to the drug were

285 added to the original gels before drying as shown in table 2 above. Blank MET films showed

286 complete transparency similar to that shown in figure 1; whereas drug loaded films

287 containing L-arg were slightly cream in colour as shown in figure 3c.

288

289 Generally, plasicised drug loaded films containing OME and L-arg (1:1; 1:2 and 1:3) showed

290 a significant difference in their visual appearance compared to unplasticised films with the

291 former showing better transparency and uniformity. Another difference observed between the

292 different formulations was that the films prepared from aqueous only gels, were difficult to

293 peel off from the Petri dish due to their thin nature. Further, the distribution of OME and L-

294 arg was more uniform in the films prepared from the ethanolic gels (10% and 20% v/v

295 EtOH). It was therefore concluded that films prepared from ethanolic gels (EtOH 20%) were

296 the most transparent and uniform which could be due to complete molecular dispersion of

297 drug (OME) and L-arg within the polymeric matrix.

298

299 Based on the visual observation and the expected characteristics for an ideal film in terms of

300 flexibility, uniformity and transparency, films prepared from ethanolic gels (20% v/v EtOH)

301 containing 1:2 ratio of OME: Larg and 0.5% w/w PEG400 was the most appropriate for

302 further investigations. It was also obvious that the addition of L-arg helped to stabilise the

303   drug within the films as can be seen by comparing figures 3b and 3c, with the latter showing

304   desired homogeneity, transparency and uniform drug distribution. Figueiras et al (23)

305   suggested that when combined together, the H atom of the L-arg was observed to be in closer

306   proximity to the nitrogen atom of OME. They also observed that the distance between the H

307   (L-arg) and the N (OME) is relatively small which increases the chances of formation of

308   hydrogen bonds between the two compounds.

309

310   *Scanning electron microscopy (SEM)*

311   SEM images of the MET films cast from gels prepared with different solvents (water, 10%

312   EtOH and 20% EtOH) with or without PEG (0.50% w/w) are shown in figure 4a. The

313   microscopic appearance of all MET films, showed continuous sheets with relatively smooth

314   and homogeneous surfaces and suggest that all the components were uniformly mixed during

315   gel formation. The plasticised films showed smooth and homogeneous surfaces whilst

316   unplasticised films showed rougher surfaces with some lumps. The surface topography of the

317   SA films was dependent on the solvent used during gel preparation. Films prepared from

318   aqueous gels showed considerably rougher surfaces than films prepared using 10% EtOH,

319   which in turn showed uneven surfaces than films prepared using 20% EtOH as shown in

320   figure 4b. This could be related to the more rapid drying of ethanolic gels during film

321   formation. Such differences in surface topography could influence the uniformity of the

322   films, because any pores or lumps in the film could affect the subsequent functional

323   performance of different formulations with respect to hydration capacity/swelling studies,

324   mucoadhesion and drug release characteristics.

325

326   *Differential scanning calorimetry (DSC)*

327   The thermogram for pure MET and SA can be seen in figure 5a, showing a broad

328   endothermic peak at between 80 - 95°C, caused by evaporation of water and no definite melt

329   or glass transition peaks. In general the thermograms of the films shown in figure 5b were

330   similar to the pure MET powder. Figure 5b further shows the different MET films [aqueous

331   and ethanolic (10% and 20% EtOH)] which were prepared using different percentages of

332   PEG 400. All the films can be characterized as amorphous, as only the broad endothermic

333   peak can be observed between 40 and 100°C which is attributed to water loss.

334

335   The DSC thermograms for pure OME, L-arg and drug loaded MET OME 1: 2 L-arg

336   0.50%PEG EtOH 20% films are shown in figure 5c. It can be observed that OME has a

melting point at 158°C and L-arg at 100°C and broad endothermic peak which can be seen at 80°C for the drug (L-arg) loaded film representing water loss and a complete absence of the melt peaks for both OME and L-arg. This suggests amorphous drug formation or molecular dispersion of both OME and L-arg within the MET film matrix.

Thermogravimetric analysis (TGA)

The TGA results of blank films (aqueous and ethanolic) are shown in table 3 indicating the percentage loss with heating, attributed to residual water present within the film matrix. Due to PEG having hydrophilic characteristics, it was expected that the residual moisture content will increase for all films with increasing PEG 400 concentration. However, this was not the case except at higher concentrations (0.50 and 0.75 % w/w of PEG) where the % content increased. It also appears that the residual water was generally lower for films prepared using ethanolic gels than those from aqueous gels which is to be expected as there was less water in the original gel and ethanol generally allows faster drying than pure water on its own. In addition, the moisture content of less than 3% in all films was considered low enough to sustain drug stability during storage though this will need to be investigated with an accelerated stability study.

Table 3: Weight loss observed for MET films cast from water, ethanol (10%) and ethanol (20%) gels containing different concentrations of PEG 400 (0, 0.25, 0.50 and 0.75 % w/w)

MET blank Films	
Films	**Weight loss (%)**
MET, 0.00% PEG, aqueous	2.77
MET, 0.25% PEG, aqueous	1.74
MET, 0.50% PEG, aqueous	2.03
MET, 0.75% PEG, aqueous	2.75
MET, 0.00% PEG, 10% EtOH	2.26
MET, 0.25% PEG, 10% EtOH	1.60
MET, 0.50% PEG, 10% EtOH	2.12
MET, 0.75% PEG, 10% EtOH	2.47
MET, 0.00% PEG, 20% EtOH	2.64
MET, 0.25% PEG, 20% EtOH	1.80
MET, 0.50% PEG, 20% EtOH	1.99
MET, 0.75% PEG, 20% EtOH	2.17

X-ray diffraction (XRD)

To investigate the crystalline/ amorphous characteristics of all initial compounds and of the films, XRD was used. Amorphous compounds generally show very broad peaks, in comparison to the sharp peaks belonging to the crystalline form. XRD can also give information about the crystalline-amorphous ratios for the various starting materials and the formulated films (24). Figure 6 shows XRD diffractograms of pure MET and PEG 400, generally indicating the amorphous nature of MET and plasticiser.. Figures 6 also shows the diffractogram of blank plasticised MET films with broad peaks indicating amorphous characteristics as was observed in the pure polymers as well as the diffractograms of pure OME, L-arg and drug loaded film (20% EtOH 0.5%PEG 1:2 OME: L-arg). As can be seen, the results demonstrate that the drug loaded film was also amorphous suggesting possible molecular dispersion of the drug. This is interesting as it confirms the DSC results previously discussed and also the fact the MET together with L-arg were able to successfully maintain the stability of OME in amorphous form within the film matrix during formulation and storage prior to analysis. These results are interesting, however, it is well known that the amorphous forms are generally unstable and have the tendency to convert back to the amorphous forms. Therefore, further physical and chemical stability studies under controlled conditions of temperature and humidity (both normal and accelerated) are required over a longer period of time (over one month) for firm confirmation of its long term stability in the current physical state.

Conclusions

Due to the poor stability of OME in aqueous environment, L-arg was required in drug loaded films as a stabilizing agent. The most promising characteristics were observed in plasticised MET films (0.50 % PEG 400) prepared from ethanolic (20% v/v) gels and containing OME: L-arg ratio of 1:2. These characteristics include; transparency, ease of peeling and flexibility of the films for further investigation. It was also confirmed that OME originally loaded in crystalline form was molecularly dispersed (amorphous) within the MET film matrix. The MET films have potential for paediatric buccal administration and will be further functionally characterized to determine its *in vitro* cell culture, *ex vivo* and *in vivo* performance.

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Legends to Figures

Figure 1: Physical appearance (digital photograph) of films prepared using different polymers, i.e., sodium alginate (SA), metolose (MET), carrageenan (CA), hydroxypropyl methylcellulose (HPMC) and methylcellulose (MC).

Figure 2: Tensile (tensile strength, percent elongation at break and elastic modulus) profiles of (a) MET films and (b) SA films containing different concentrations of PEG and cast from different solvent systems.

Figure 3: (a) Degradation of OME in aqueous gel as evidenced by change in colour to red within 20 minutes of preparation; (b) films prepared from gels containing OME without L-arg showing OME degradation and (c) films prepared from gels containing OME stabilized with L-arg.

Figure 4: Scanning electron microscope images of (a) MET films cast from aqueous and ethanolic (10% and 20% v/v) gels containing different concentrations of PEG 400 (0% and 0.50% w/w) and (b) SA films cast from aqueous and ethanolic (10% and 20% v/v) gels containing no PEG 400.

Figure 5: DSC thermograms of (a) pure PEG and pure MET, (b) representative optimum blank, plasticized (0.50 % w/w PEG 400) MET films cast from ethanolic (20% v/v) gels and (c) pure L-arg, pure OME and drug loaded MET film prepared from ethanolic (20% v/v) gels containing OME: L-arg (1:2) and PEG 400 (0.50% w/w).

Figure 6: XRD diffractograms for pure MET, pure PEG, pure OME, L-arg, blank MET films, and drug loaded MET films, showing amorphous drug distribution in the drug loaded films.
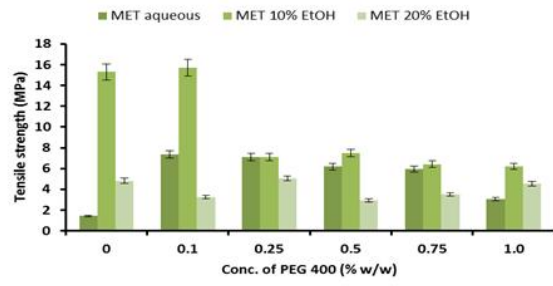
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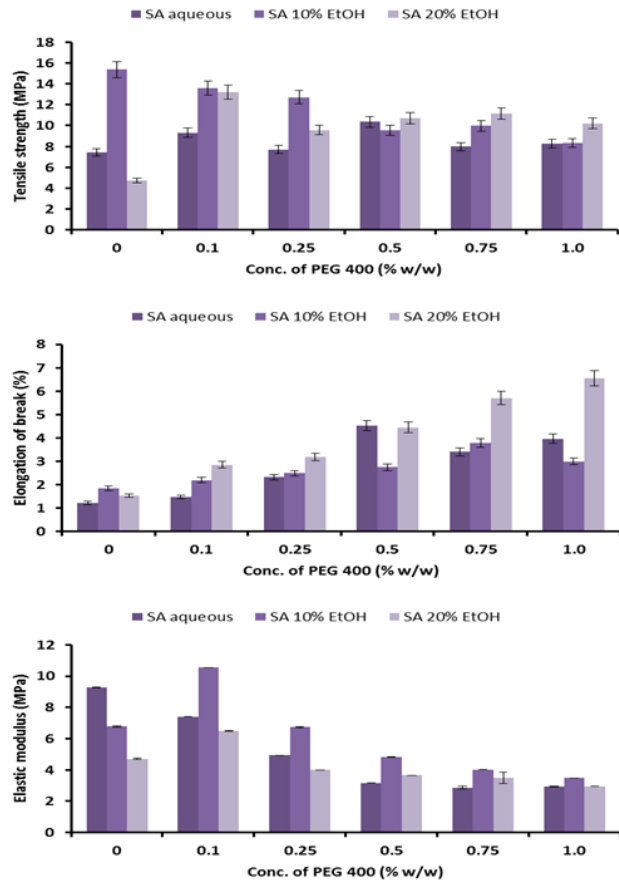505
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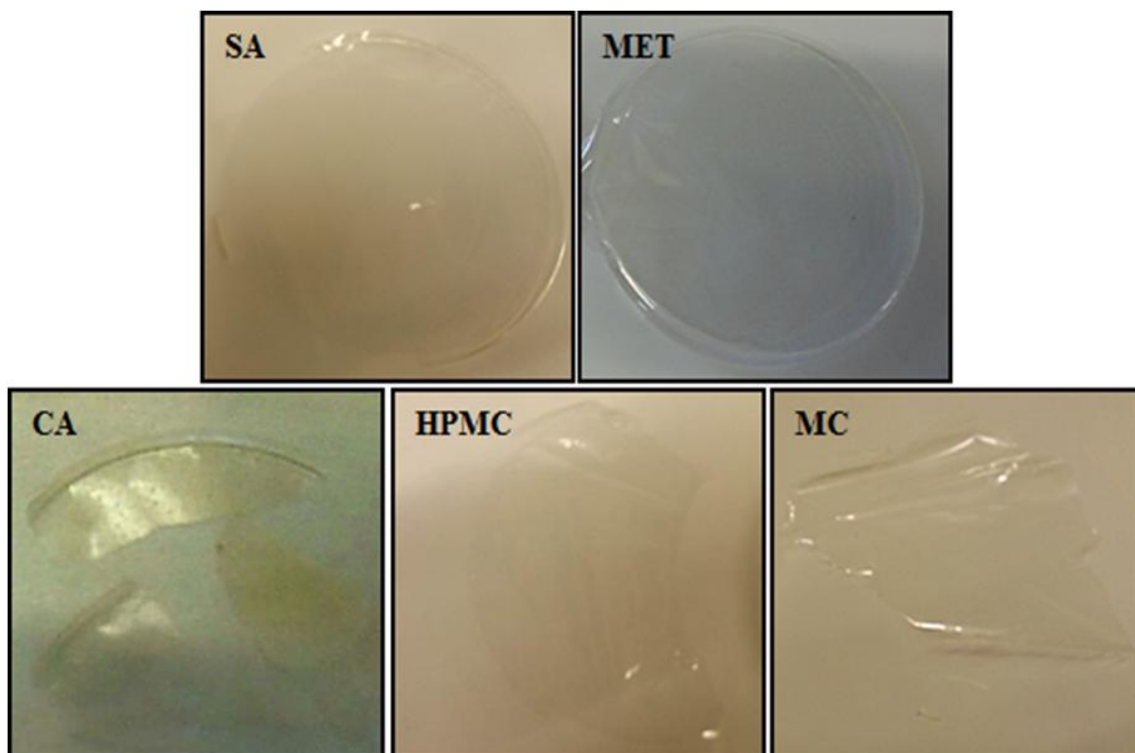
Figure 1

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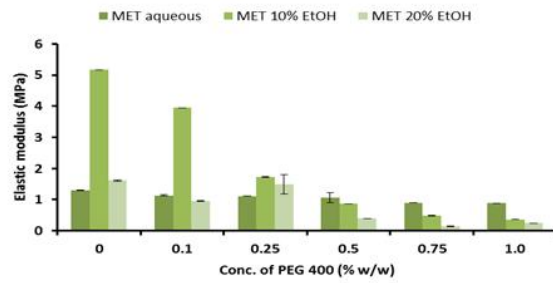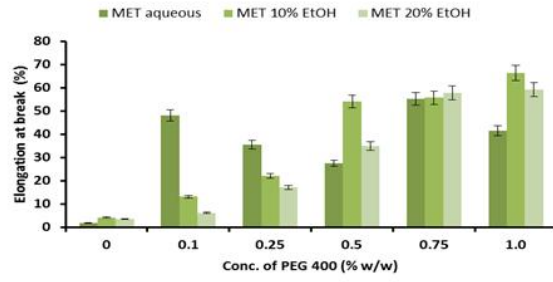
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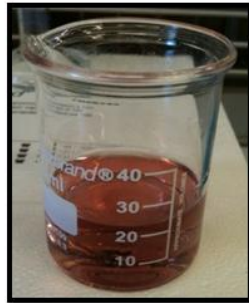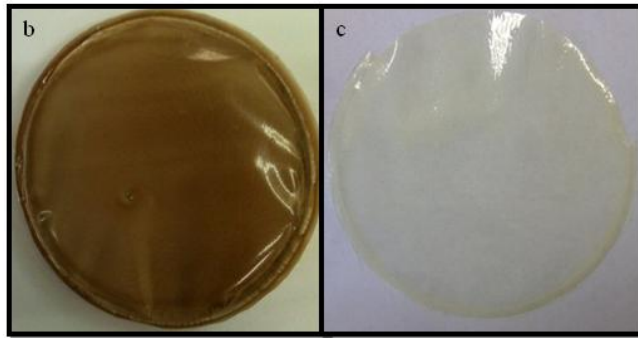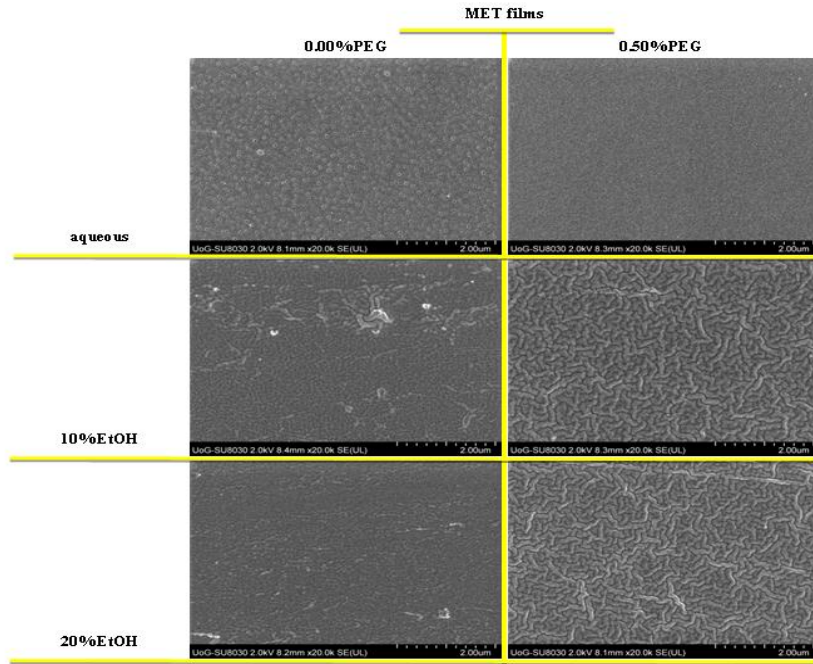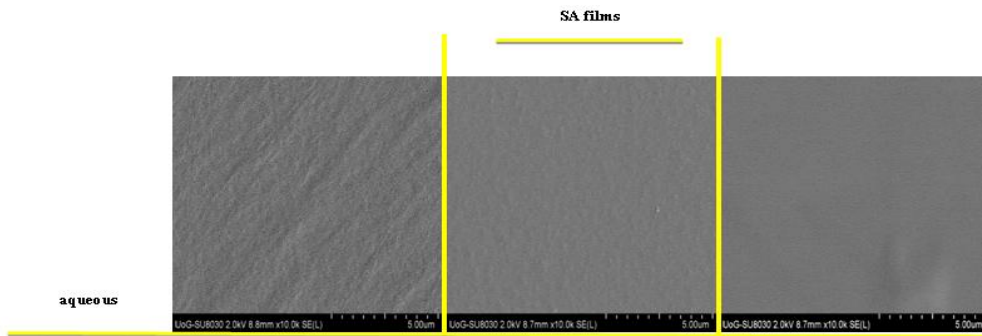553
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Figure 3a

Figure 3b & 3c

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MET films

0.00%PEG　　　　　0.50%PEG

aqueous

10%EtOH

20%EtOH

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586　　a
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SA films

aqueous

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589　　b

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591　　Figure 4

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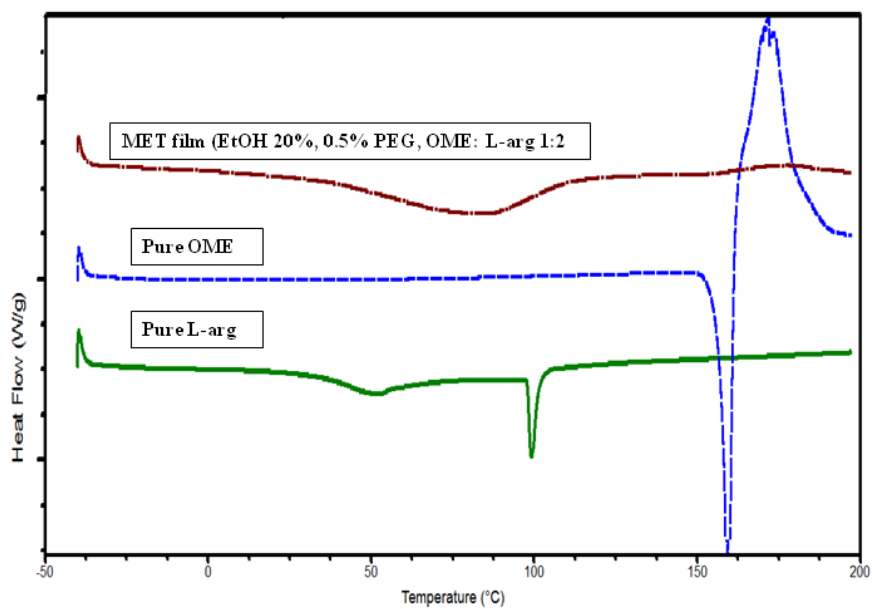594   a
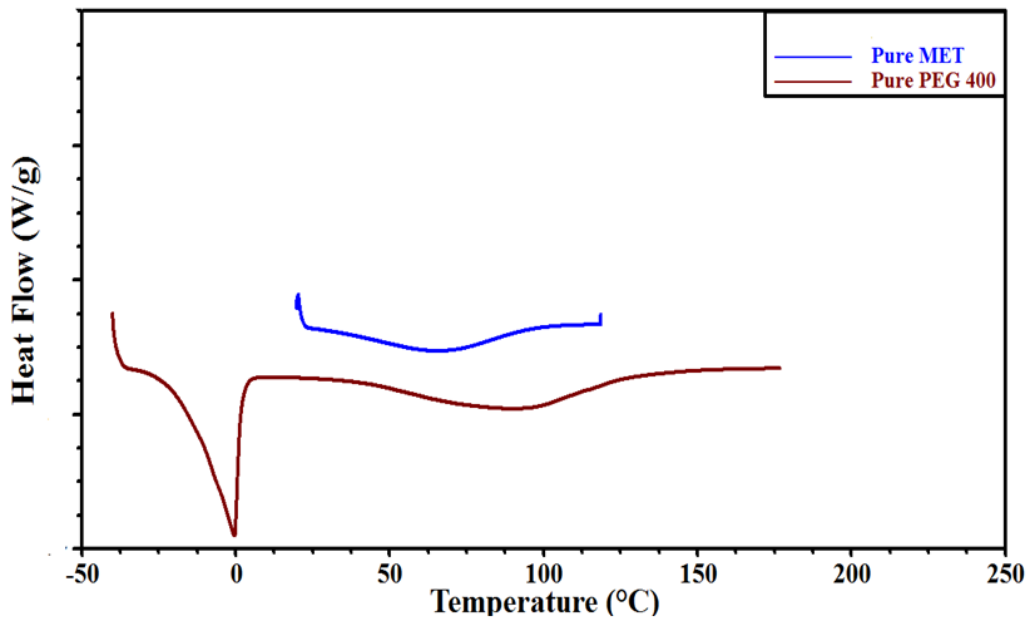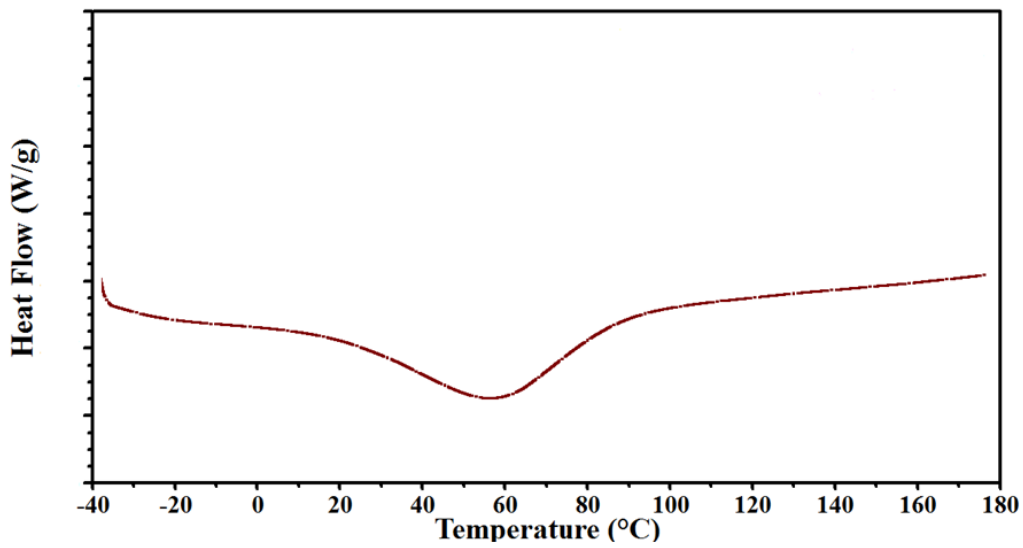
Figure 5 b

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Figure 5c

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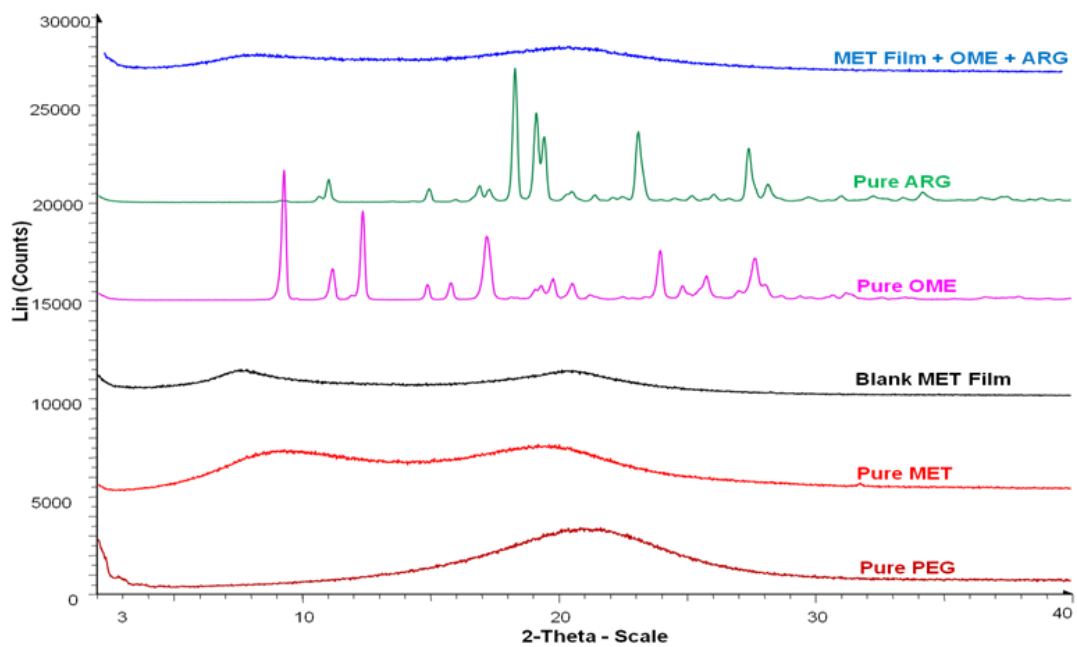601   Figure 5
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628   Figure 6