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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

52 **Introduction**

53 Amongst all the established routes of drug administration, the oral route is perhaps the most
54 preferred for both patients and healthcare providers compared to other routes such as
55 injections. However, this route of administration has disadvantages including enzyme
56 degradation within the gastrointestinal tract which prohibits oral administration of certain
57 classes of drugs such as peptides and proteins. Evidence has shown that the oral mucosa is
58 relatively permeable with a rich supply of blood and shows a short recovery time after stress
59 or damage. Further, it also lacks Langerhans cells which allow the oral cavity to be tolerant of
60 any potential allergens (1). Drug administration within the oral mucosa is generally classified
61 into sublingual and buccal delivery. Among all the trans-mucosal routes, the buccal mucosa
62 has excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa,
63 hence suitable for the administration of retentive dosage forms (2-3). Direct access to the
64 systemic circulation through the internal jugular vein bypasses hepatic first pass metabolism
65 leading to relatively high bioavailability compared to the GI tract. Additionally, the buccal
66 mucosa has a high surface area (50.2 cm²) and a thin membrane (500–600 μm) which can
67 contribute to rapid and extensive drug absorption (4).

68

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

80

81 Numerous buccal delivery systems in the form of tablets, liquids and semi-solids have been
82 reported in the past decades yet only a limited number of these have reached the market (7).
83 The necessity of recurrent dosing might possibly arise due to the flushing activity of saliva,
84 chewing and the ingestion of food materials which results in the rapid expulsion of drugs.
85 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

144

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

146 Due to the breakdown of OME following gel formation, L-arg was used as a stabilising agent
147 to prevent drug degradation. Table 2 shows the details for the different ratios of OME and L-
148 arg in the gel formulations which were investigated. This step was performed by using
149 different amounts of L-arg within the gel whilst keeping the original OME concentration
150 (0.10% w/w) constant. The gels were prepared as above with L-arg and OME dissolved in the
151 solvent before addition of MET and PEG 400.

152

153 Table 2 – Different OME: L-arg ratios in the MET gel formulations for preparing both
154 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

155

156 *Characterization of the films*

157

158 *Tensile characterisation by texture analysis*

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

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

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

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

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.

201 *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 $\text{CuK}\alpha_{1\&2}$ primary beam ($\lambda=1.54184 \text{ \AA}$)
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 2θ 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

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, plasticised 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: L-arg 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

337 melting point at 158°C and L-arg at 100°C and broad endothermic peak which can be seen at
338 80°C for the drug (L-arg) loaded film representing water loss and a complete absence of the
339 melt peaks for both OME and L-arg. This suggests amorphous drug formation or molecular
340 dispersion of both OME and L-arg within the MET film matrix.

341

342 *Thermogravimetric analysis (TGA)*

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

354

355 Table 3: Weight loss observed for MET films cast from water, ethanol (10%) and ethanol
356 (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

357

358

359

360 *X-ray diffraction (XRD)*

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

380

381 **Conclusions**

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

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468 **Legends to Figures**

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

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

476

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

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482 **Figure 4:** Scanning electron microscope images of (a) MET films cast from aqueous and
483 ethanolic (10% and 20% v/v) gels containing different concentrations of PEG 400 (0% and
484 0.50% w/w) and (b) SA films cast from aqueous and ethanolic (10% and 20% v/v) gels
485 containing no PEG 400.

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

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

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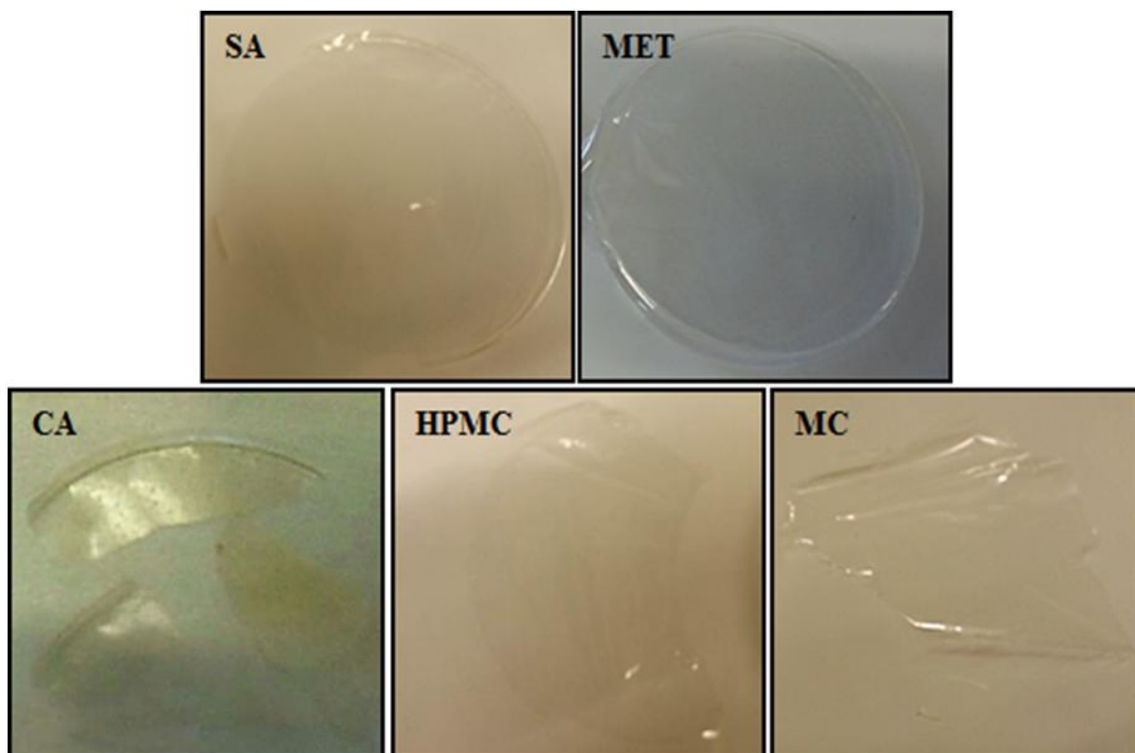
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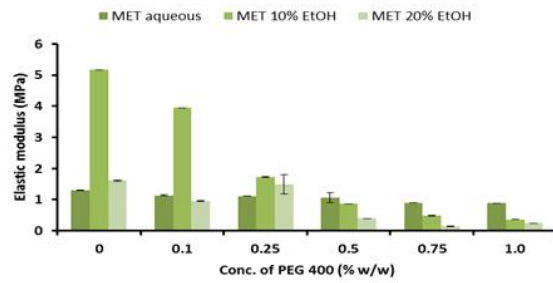
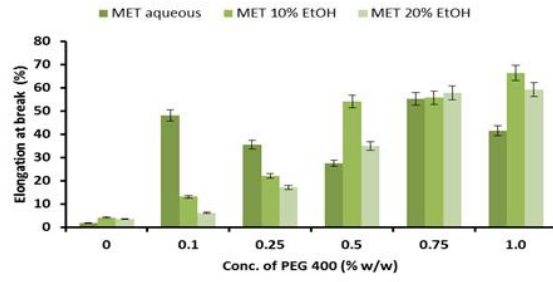
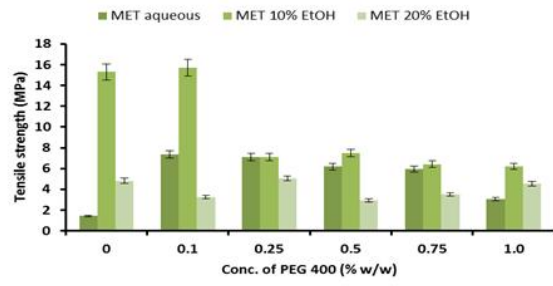
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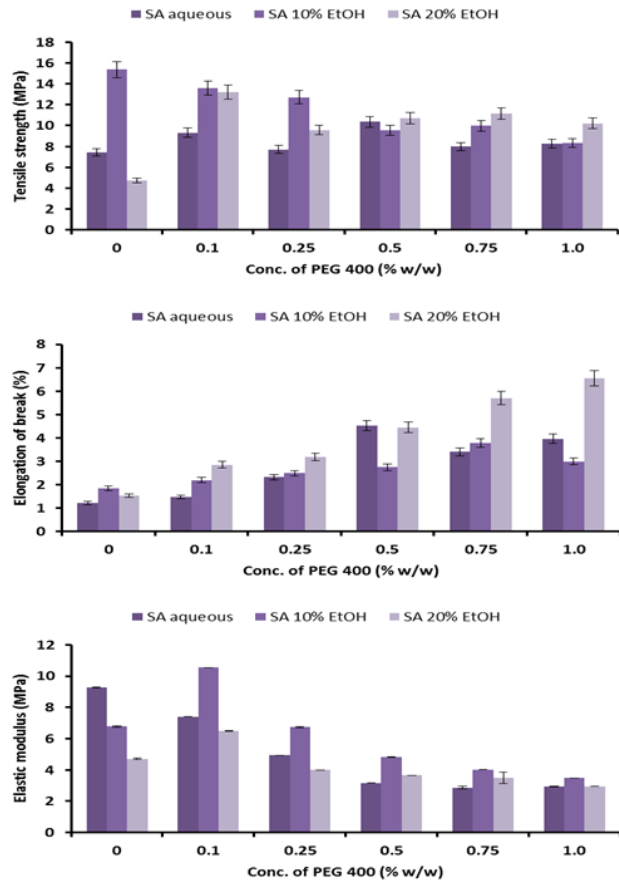


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Figure 1



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Figure 3a

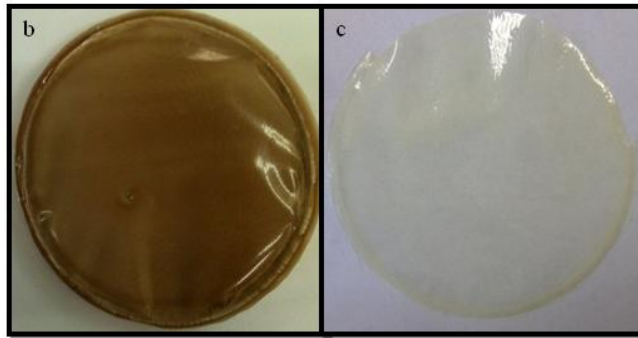
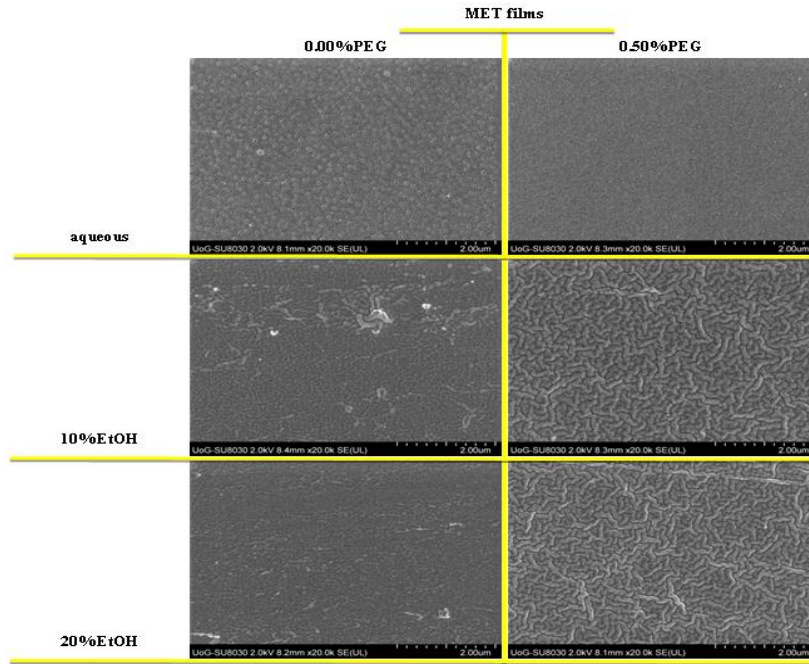
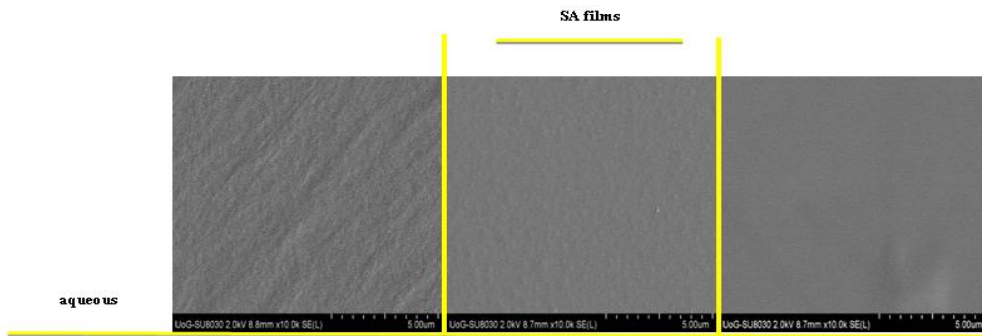


Figure 3b & 3c

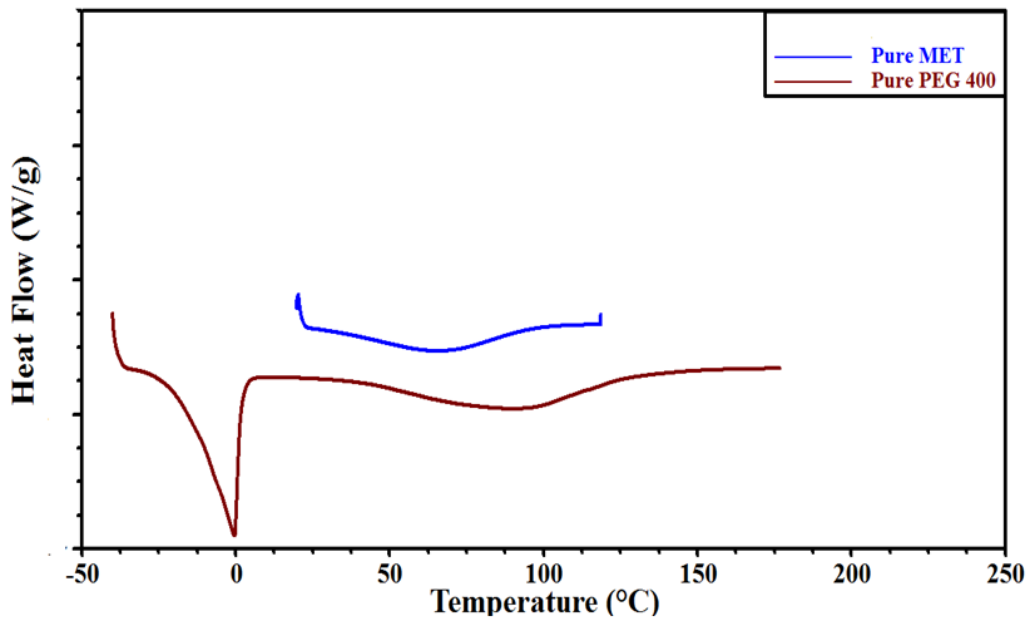
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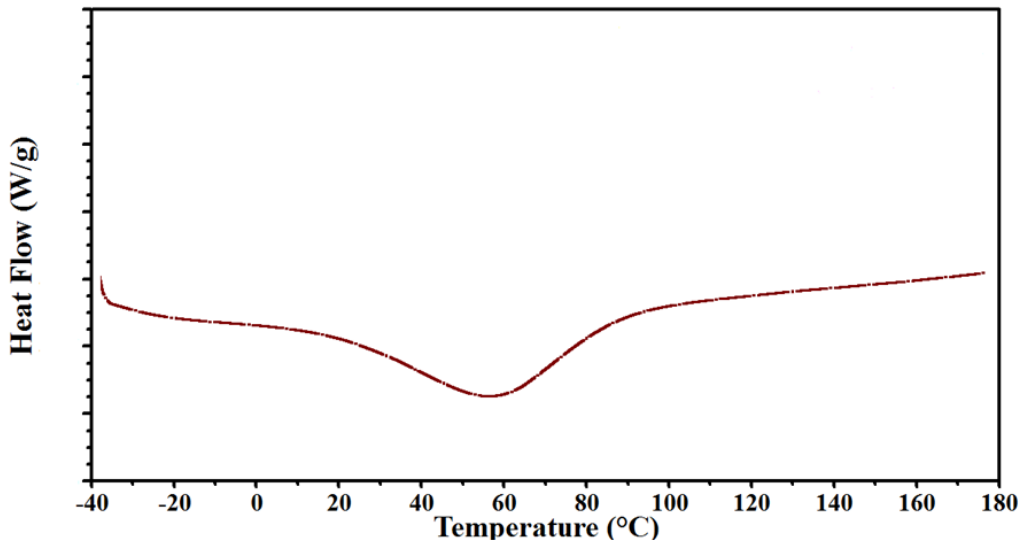


Figure 5b

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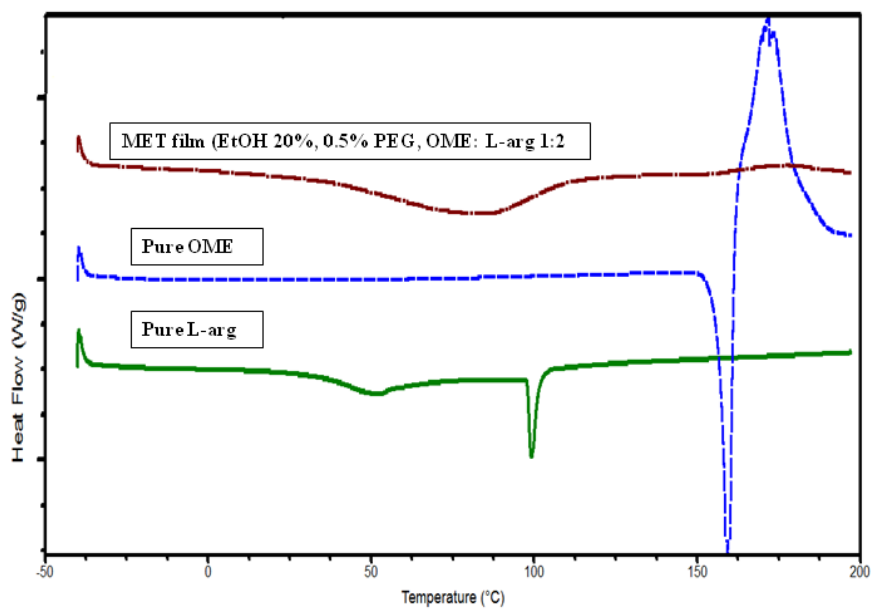


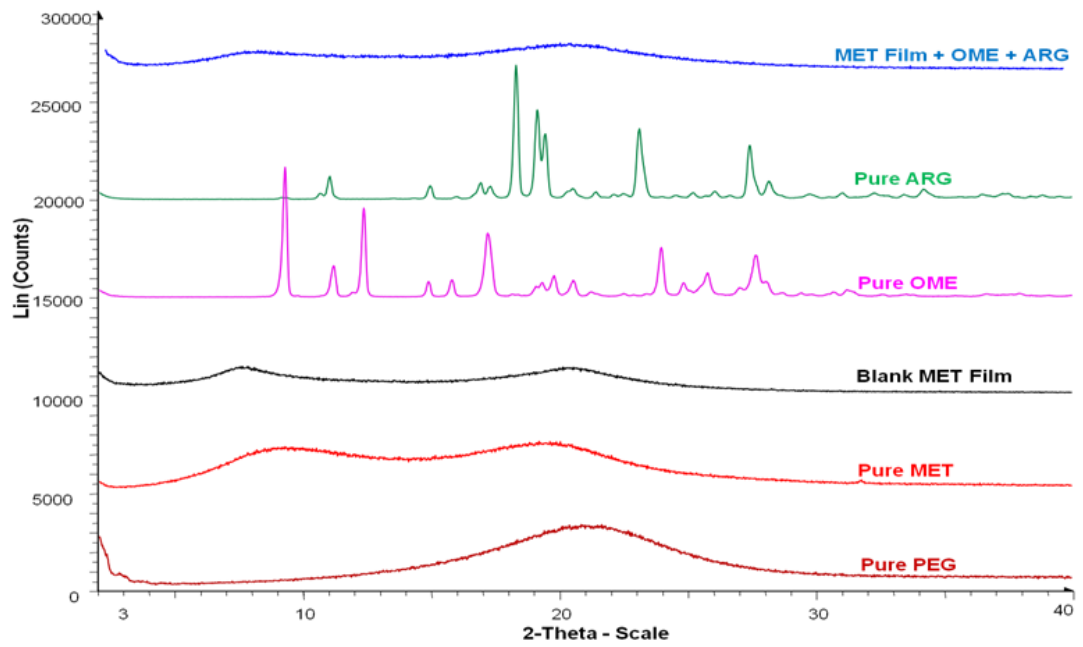
Figure 5 c

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628 Figure 6