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Tragacanth and xanthan gum natural polymers for formulation of clotrimazole mucoadhesive gel

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ABSTRACT. Clotrimazole is an antifungal agent, widely used in vulvovaginal and oropharyngeal candidiasis. Currently available clotrimazole (especially vaginal) dosage forms, have some limitations, including: leakage, messiness and low residence time, which leads to poor patient compliance. Therefore, in this study, a clotrimazole mucoadhesive gel has been developed as a suitable strategy due to their high water content, increased local retention time, lubrication and patient compliance. Xanthan gum and tragacanth with different portions were utilized as natural mucoadhesive gel forming polymers. Gel formulations were subjected to physico-chemical evaluations including gel viscosity, FTIR spectroscopy, spreadability, scanning electron microscopy (SEM) images of hydrogel chains, and release kinetic. Results demonstrated that among 8 developed formulas, formulation F_1 showed the appropriate properties including controlled drug release (63.13% in 6h) with higuchi release kinetic, higher mucoadhesion (77.71 dyne cm^{-1}) and drug content (94.47%) and relatively low spreadability (3.5 cm) which is suitable for local drug delivery. FTIR spectroscopy revealed there is not incompatibility between clotrimazole and other excipients in formulations. Combination of natural polysaccharides can form a proper mucoadhesive gel matrix for delivery of synthetic or natural drugs.

Keywords: clotrimazole; mucoadhesive gel; xanthan gum; tragacanth; natural polymers.

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Introduction

Candida is usually an opportunistic fungal pathogen and can cause local and systemic mycoses in predisposed people, commonly affecting immunocompromised patients and those undergoing prolonged antibiotic treatment. About 150 species of Candida have been recognized, out of them *C. albicans* is one of the most pathogenic species and it cause candidiasis (Kumar, Karthik, & Rao 2010).

Most Candida infections can be treated with topical administration of antifungal drugs such as clotrimazole, miconazole, nystatin, tioconazole, etc. Clotrimazole (1-[(2-chlorophenyl)diphenylmethyl]-1H-imidazole), an imidazole derivative, is a widely used drug with a wide spectrum of antifungal activity, particularly against candidiasis (Manca et al. 2019; Soriano-Ruiz et al. 2019). It acts by inhibiting cytochrome 14α-demethylase enzyme of the fungal cells responsible for cell wall synthesis (Santos et al. 2013). It has very well-tolerated topical products with few side effects and is widely used as a topical treatment for tinea pedis, vulvovaginal and oropharyngeal candidiasis. Currently, clotrimazole is available as conventional topical formulations such as cream, lotion and troches (Gupta, Sharma, & Chauhan, 2017).

The impediment of the conventional formulations eg. mouthwash, gel, etc. in oral candidiasis is the easy removal of drug by the tongue motions and saliva secretion (Paderni, Compilato, Giannola, & Campisi, 2012). Also in vaginal candidiasis, currently available vaginal dosage forms (such as solutions, creams, foams, tablets and rings) have some limitations, including: leakage, messiness and low residence time, which leads to poor patient compliance. Hence, mucoadhesion has been proposed as a suitable strategy for mucosal disease treatment to improve *in vivo* performance of antifungal formulations ensuring a long permanence of the loaded therapeutic agent at the site of infection (Peppas & Buri, 1985). Among them, gels have received great attentions due to their high water content (Khan et al., 2020) and rheological behavior causing increased vaginal retention time, lubrication and patient compliance (Bonferoni et al., 2006; Ramadan, Elbakry, Esmaeil, & Khaleel, 2018). Gels are also easy to manufacture and scale up and are preferred vaginal drug delivery system among ladies (Braunstein & Wijgert, 2005; Vandebosch et al., 2004).

Natural biodegradable polysaccharide-based gels displaying excellent properties have already been reported by several researchers. They are biocompatible or non-toxic in nature, produced by living organisms with no adverse impact on environmental health. They are low in cost & easily available (Heydary, Karamian, Poorazizi, Khandan, & Heydaripour, 2015; Salamanca, Yarce, Moreno, Prieto, & Recalde, 2018; Gandhi, Verma, Imam, & Vyas, 2019; Tanan, Panichpakdee, & Saengsuwan, 2019).

Tragacanth Gum (TG) is a dried exudation obtained from the stems and branches of Asiatic species of Astragalus, (Mohammadifar, Musavi, Kiumarsi, & Williams, 2006). TG has been accepted since 1961 as ʻgenerally recognized as safe' (GRAS) at the level of 0.2-1.3% and in Europe has E-number E413 on the list of additives approved by the Scientific Committee for Food of the European Community (Saffari, Farzi, Emam-Djomeh, Moini, & Mohammadifar, 2013). Itʻs safety has been approved among mutagenic, carcinogenic, allergenic, teratogenic and toxicological effects on the human body and cell growth (Ghayempour, Montazer, & Rad, 2015).

TG is widely used in various fields such as food, pharmaceuticals, biomedicals and cosmetics acting as the stabilizer, emulsifier, thickener, cell matrix, fat replacer and cross-linking agent (Firooz, Mohammadifar, & Haratian, 2012). Several researches have determined the physical, chemical and biological characteristics of TG including structure, thermal behavior, emulsifying,, viscosity, acidity, stability, and also rheological, antibacterial, biocompatibility and biodegradability (Debon & Tester, 2001; Zohuriaan & Shokrolahi, 2004; Chenlo, Moreira, & Silva, 2010; Farzi, Yarmand, Safari, Emam-Djomeh, & Mohammadifar, 2015). In recent years, several works are reported on the application of TG in the wound and burn dressing (Nayeb Morad, Rashidi, Khajavi, Rahimi, & Bahador, 2018), synthesis of various nanoparticles (Kora & Arunachalam 2012; Hajizadeh, Farhadi, Molaei, & Forough, 2020; Tavakoli, Shadizadeh, Hayati, & Fattahi, 2020), biosensor (Qasemi & Ghaemy, 2020a), superabsorbent hydrogel(Qasemi & Ghaemy, 2020b), cell matrix (Ranjbar Mohammadi, Kargozar, Bahrami, & Rabbani, 2020) and drug delivery systems (Niknia, Kadkhodaee, & Eshtiaghi, 2020; Verma, Negi, Pathania, Anjum, & Gupta, 2020). Since the TG is one of the most acid-resistant polysaccharides, it seems to be an efficient natural polymer for vaginal drug delivery due to its physiological acidic environment.

Xanthan gum (XG) is an anionic branched biopolymer resulting from the aerobic fermentation of either sugar cane or corn in the presence of the *Xanthomonas campestris* bacteria (Pawlicka et al., 2019). The molecular structure of XG is similar to the cellulose, with the exception of the trisaccharide side chains on the alternate sugar units. These parts of the chains are composed of d-glucuronic acid ring in between d-mannose acetate, attached to the main chain, and d-mannose pyruvate as a terminal ring. The d-glucuronic acid and d-mannose pyruvate are responsible for XG anionic character (Kumar, Rao, & Han, 2018). Xanthan solutions is known as a thickening agent with pseudoplastic behavior and high stability over a wide range of temperature and pH and in the presence of various types and amounts of salts (Andreopoulos & Tarantili 2001). Xanthan gum has been used widely in many important applications such as cosmetic and pharmaceutical industry as suspending agent, emulsifying agent. Xanthan gum is extensively used for enhanced oil recovery in the petroleum industry because it is drag reducing agent with good shear stability (Pandey & Mishra 2011).

To the best of our knowledge, although there are various dosage forms of clotrimazole, there is no mucoadhesive clotrimazole gel available in market. Therefore, this study was designed for formulation and physico-chemical evaluations of clotrimazole mucoadhesive gel for both oral and vaginal indications. Gel forming polymers are chosen only from natural gums (tragacanth and xanthan gum) due to all their advantages specially ecosystem friendliness and high biocompatibility.

Material and methods

Materials

Tragacanth and xanthan gum were purchased from Gol Darou Co, Tehran, Iran. Clotrimazole was obtained from Behvazan pharmaceutical Co, Rasht, Iran. Propylene glycol (PG), myrj52 and sodium benzoate were procured from Sigma-aldrich, Germany. Dialyzes bags with a molecular weight cutoff of 14kDa were purchased form Sigma (Steinheim, Germany). All gel formulations were prepared in deionized water.

Ethical approval

The study protocol was approved by research committee of Guilan University of Medical Sciences by the ethics code of IR.GUMS.REC.1396.282.

Preparation and characterization of the mucoadhesive gel

According to the study design (Table 1) proper amount of each polymer was mixed with deionized water in a 250 mL beaker. The colloidal solution was stirred with magnetic stirrer at 500 rpm. Clotrimazole and myrj 52 and other excipients were dissolved in determined volume of deionized water, separately. Finally, clotrimazole and polymeric colloidal solutions were mixed and adjusted to 100 mL.

Table 1. Natural polymers and other excipient composition in formulations F_1-F_8.

Formulations	Clotrimazole	Xanthan gum	Tragacanth	Na benzoate	PG	Myrj 52
F_1	1	3.5	0.5	0.25	5	1
F_2	1	3	0.5	0.25	5	1
F_3	1	2.5	0.5	0.25	5	1
F_4	1	2	0.5	0.25	5	1
F_5	1	1.5	0.5	0.25	5	1
F_6	1	1	0.5	0.25	5	1
F_7	1	5	-	0.25	5	1
F_8	1	-	5	0.25	5	1

- Visual examinations: formulations F_1-F_8 were visually evaluated among color, clarity, homogeneity, presence of particles or polymer clamps.

- Viscosity studies: viscosity of samples was measured using a DV-3 con viscometer (Brookfield, USA). 50 ml of samples were applied to viscometer container in 37°C (n=3) (Pandey et al. 2020).

- Gel spreadability: 0.5 g of each gel formulations was placed on a circle glass plate with 1cm diameter and another glass plate was placed on the gel. A 50 g weight was placed on upper glass for 5 minutes. The spreading area was calculated using the measurement of increase in gel diameter (n=3) (Deuschle, Deuschle, Bortoluzzi, & Athayde, 2015; Dantas et al., 2016).

- FTIR Spectroscopy: A FTIR spectrophotometer (Thermo Nicolet, model: Nexus670, USA) was used to examine the probable incompatibilities between clotrimazole and excipients. Clotrimazole, TG, XG and Formulations F_1 (as the combination of API and excipients) where evaluated. FTIR Spectra were collected at a resolution of 4 $cm^{-1}$and given as the ratio of 21 single beam scans to the same number of background scans in pure KBr (Fidalgo & Ilharco, 2001).

- Drug content: 1 g of gel was vigorously stirred with 100 ml citrate buffer, using sonicator and vortex resulting in a transparent solution after filtration. Then the filtrate was subjected to UV spectrometry in 230 nm (n=3) (Kumar & Verma, 2010).

- Scanning electron microscopy analysis: Polymer chain morphology was investigated by FESEM Sigma VP (Zeiss, Germany) with an accelerating voltage of 10 kV under vacuum conditions. For sample preparation, gels were air dried at 25°C in a desiccator and dried gels were gold sputter coated before FESEM (Schemehorn, González-Cabezas, & Joiner, 2004).

Mucoadhesive properties

Mucoadhesion study was performed according to Tasdighi's method (Tasdighi, Azar, & Mortazavi, 2012) with some modifications. 0.5 g of each gel formulations (A) was placed between two circle glasses (B) covered with sheep intestinal mucus (C). Bottom glass was fixed in a crystallizer and top glass was linked to a balance measuring the required force for detachment of the gel from mucosal membrane. The test was performed in phosphate buffer medium pH=4.5 and 37°C (n=3).

Pharmacokinetic study

- *In vitro* release profile: The in vitro release was performed using 14 kDa Dialysis tubing Cellulose Membrane. Membrane was soaked in distilled water for 24hrs, before experiment. 5 g of each formulation was packed in dialysis tube and placed in 200 mL citrate buffer (pH=5) and ethanol (70:30) as receptor medium, in 37°C. Medium was stirred at 100 rpm during the release test and samples were withdrawn at certain time intervals of 0.5, 1, 2, 4, and 6hrs. Content of clotrimazole in each sample was analyzed with UV spectrophotometry (PerkinElmer, USA) in 230 nm (Kumar & Verma, 2010).

- Drug release kinetic: The *in vitro* release data was incorporated to investigate the release kinetics of formulations F_1, F_6, F_7 and F_8 using various mathematical kinetic models. Release kinetic was evaluated in

formulations F_1, F_6, F_7 and F_8 due to higher variation in their polymeric proportion (referring to table 1), supposing probable difference in release mechanisms. Evaluated models included Zero order, First order, Higuchi and Korsmeyer-Peppas which are previously explained in (Ngwuluka, Kyari, Taplong, & Uwaezuoke, 2012)

Statistical analysis

For comparison between 8 formulations, data obtained from physico-chemical evaluations (gel spreadability, drug content and mucoadhesion) was subjected to one way ANOVA. In cases in which significant differences existed in the ANOVA test, Tukey post-hoc test was used to specify those samples having significant differences with each other. In all tests, p-value ⩽0.05 was considered as significant.

Result and discussion

According the Table 1, gelling agents (polymers) were slowly dispersed in water with range of 0-5% for xanthan gum and tragacanth with a fixed amount of 0.5%. Both polymers have been incorporated with 5% w v^{-1} in F_7 and F_8, to be comparable in evaluations.

Preparation and characterization of the mucoadhesive gel

- Visual examination: revealed that all formulations where homogenous in texture, with a creamy color which was due to presence of dispersed active pharmaceutical ingredient (API) particles.

- Viscosity: also influences the gel spreadability, drug release rate and mucoadhesion. Viscosity of all formulations are listed in Table 2. Results showed that from F_1 to F_6 viscosity gradually decreases due to decrease in total polymer concentration (from 4 to 1.5%) in which the TG percent is fixed (0.5%) and XG percent reduces. F_7 and F_8 showed higher viscosity as a result of higher polymer concentration (5%) and as other studies investigated, F_7 with the highest viscosity confirmed that XG forms more viscous gel in comparison with TG in equal polymer percent (Mohammadian & Alavi 2016).

- Spreadability results: showing an exact reverse behavior with viscosity are presented in Table 2. Statistics showed the significant difference between formulations, except F_1 and F_2 in which F_1 showed lower spreadability (Tukey Post Hoc) but the difference was not significant.

Table 2. Physical properties of formulations F_1-F_8.

Formulation	Viscosity (cp) ±SD	Spreadability (cm)±SD	Mucoadhesion (dyne cm^{-2})±SD	Drug content (%) ±SD	CDR** in 6 h (%)
F_1	17800	3.5±0.2	77.71±1.96	94.47±0.45	63.13
F_2	15900	3.8±0.26	75.59±2.32	91.73±0.92	67.6
F_3	12700	4.1±0.2	74.84±2.70	91.65±0.57	72.22
F_4	12500	4.5±0.15	69.25±2.37	89.78±0.52	81.45
F_5	11400	4.5±0.2	66.47±3.58	89.34±1.46	86.73
F_6	8100	4.6±0.1	54.49±2.85	87.42±0.35	95.29
F_7	*	2.2±0.17	83.67±2.18	96.49±1.05	98.36
F_8	16800	2.6±0.17	87.38±1.77	99.65±1.13	79.35

*Due to very high viscosity, it was not measurable by the apparatus. **Cumulative drug release

- FTIR spectra: for pure clotrimazole, formulations F_1 and F_6 are presented in Figure 1 (a, b, c respectively) and positions of peaks are compared. Aromatic C-H bending (758 cm^{-1}), C=N stretch (1488 cm^{-1}), and aromatic C=C stretch (1534 cm^{-1}) and aromatic C-H stretch (3167 cm^{-1}) which are index peaks corresponding to clotrimazole are present in F_1 and F_6 final formulations spectrum. The FTIR spectra of pure API and final formulations showed that the position of characteristic peaks where not altered after incorporation in formulations confirming the absence of probable interactions between drug and excipients. Similarly, in other studies no significant interaction was found between clotrimazole and chitosan (Grimling,Karolewicz, Nawrot, Włodarczyk, & Górniak, 2020), hydroxypropylmethylcellulose, sodium carboxymethylcellulose and Carbopol (Gupta, Natasha, Getyala, & Bhat, 2013).

- Drug content: in an acceptable range of API, ensures the producer and consumer about receiving the adjusted or necessary dose. Since there is no defined monograph for vaginal clotrimazole gel in pharmacopeias, the prevalent range of 90-105% was considered as acceptable in this study. Drug content of each formulation is presented in Table 2. Statistical analysis for F_1 to F_8 revealed that there is significant difference between all formulations.

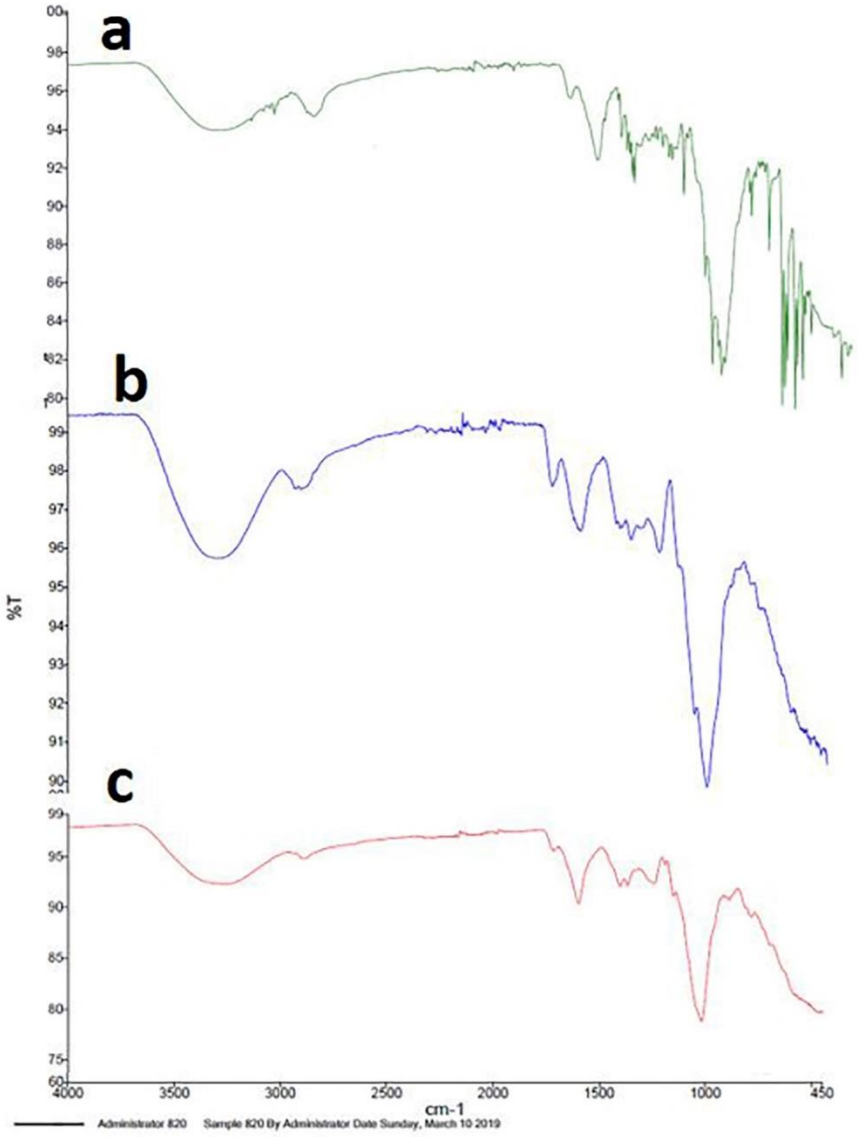

Figure 1. FTIR spectroscopy of a) pure clotrimazole, b) Formulation F_1, c) formulation F_6 with common peaks of 758, 1488, 1534 cm^{-1}.

- Scanning Electron Microscopy (SEM): characterized the polymeric chain micro-morphology of hydrogel. Samples F_7 and F_8 which were simply made of XG and TG, respectively and F_1 with highest amount of XG (3.5%) and 0.5% TG and F_6 with lowest amount of XG (1%) and 0.5% TG, were subjected to SEM. Figure 2 shows a homogenous linear morphology of chains surrounding API for F_7 (Figure 2a) and a relatively smoother morphology for F_8 (Figure 2b) while in F_1 and F_6 a kind of polymeric chain integration is observed (Figure 2 c and d). It seems that formulations containing both polymers show special polymeric interactions due to probable hydrogen or van der Waals bonds. SEM images of prior investigations also showed higher polymeric entanglements while using two or more polymers in one formulations for example cationic tapioca starch–xanthan gum mixture in comparison with cationic tapioca starch (Chaisawang & Suphantharika, 2005) or incorporation of anionic tapioca starch-xanthan gum mixture compared to anionic tapioca starch which presents higher polymeric interactions in SEM images (Chaisawang & Suphantharika, 2006). As clotrimazole is a highly lipophile API with log P above 5, it's dispersed in hydrogel and crystals are observed in all formulation's SEM results.

Mucoadhesive properties

Mucoadhesion studies showed that similar to viscosity, increase in total polymer concentration, increases the mucoadhesion and there was a statistically significant difference between all formulation's viscosity. This finding was confirmed by previous studies such as addition of XG to TG/chitosan polyelectrolyte complexes-based hydrogels which resulted in formation of a more viscous hydrogel with improved mucoadhesiveness and mechanical strength for buccal application (Potaś, Szymańska, Basa, Hafner, & Winnicka, 2021). In

another study, XG was incorporated in formulation of mucoadhesive buccal patches of zolmitriptan. Results revealed that with an increase in concentration of XG, bioadhesion force increased (Shiledar, Tagalpallewar, & Kokare, 2014). Therefore, mucoadhesion decreased from F_1 to F_6 (77.71-54.49 dynecm^{-2}). F_7 and F_8 with highest polymer concentration (5%) showed higher mucoadhesion, noting that TG revealed higher adhesion in comparison with XG in equal polymer concentration as was observed previously in (Parvinroo, Eslami, Ebrahimi-Najafabadi, & Hesari, 2020) (Table 2).

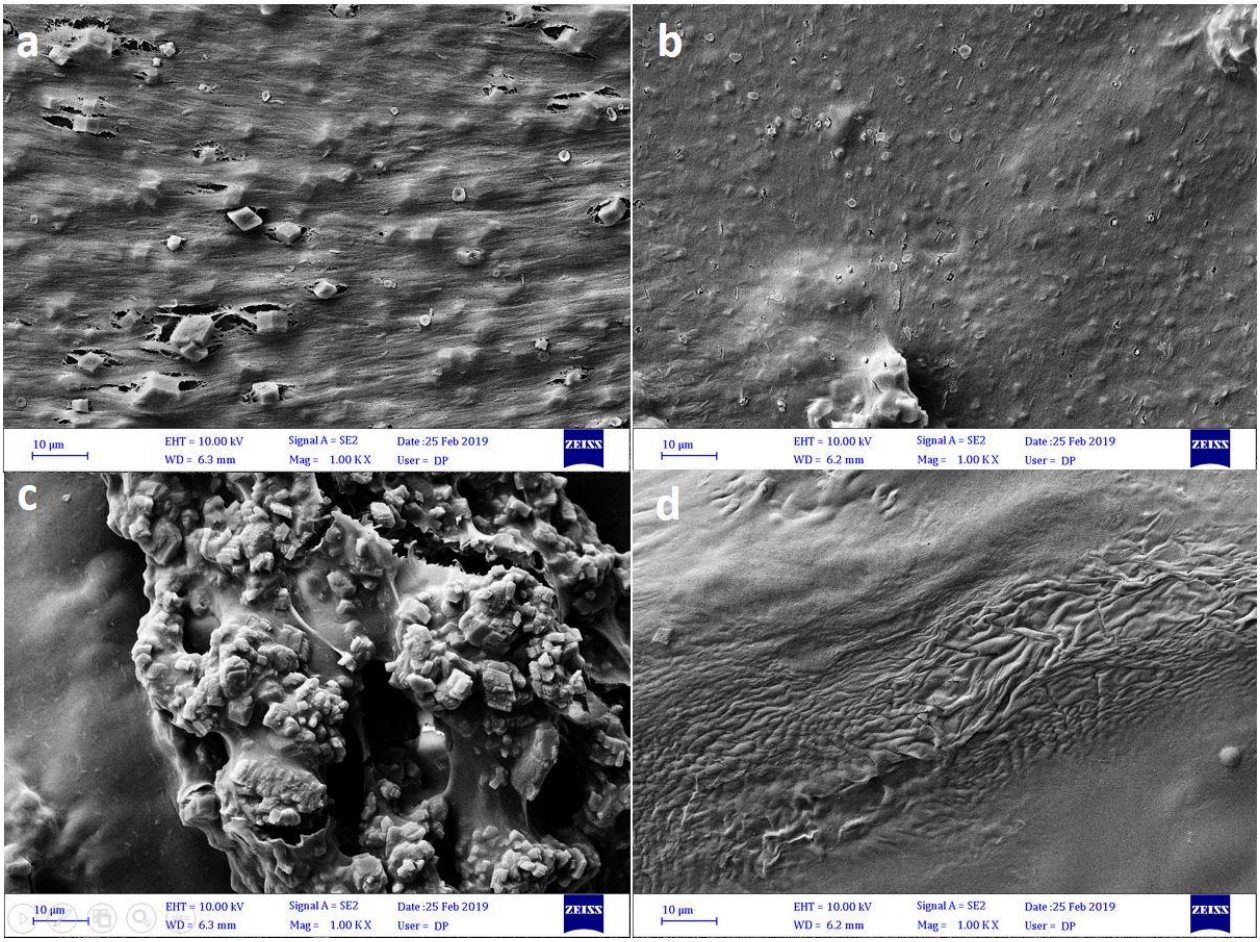

Figure 2. SEM image of hydrogel polymeric chain morphology in a) F_7: XG (5%). b) F_8: TG (5%). c) F_1: XG (3.5%) and TG (0.5%). d) F_6: XG (1%) and TG (0.5%).

Pharmacokinetic study

- *In vitro* release profile: of clotrimazole was evaluated for all formulations in citrate buffer (pH=5) and ethanol (70:30) in 37°C. F_1 to F_8 release profiles are presented in Figure 3. Based on cumulative release percent, F_6 showed the highest (95.29%), while F_1 showed the lowest (63.13%) release rate in 6 hours. Since, F_1 to F_6 gels are composed of two polymers, decrease in total amount of polymers leads in increasing the release rate from F_1 to F_6. On the other hand, comparing the release rate of F_7 and F_8 reveals that TG has a more retardant effect on drug release than XG as reported by Salamanca CH (Salamanca et al., 2018). However, total polymer concentration in F_7 and F_8 is higher than F_1 to F_6, their drug release rate is higher than F_1, F_2 and F_3. It maybe hypothesized that these two polymers show some synergistic effect in drug release rate control, when combined. Some synergistic effects were observed in XG in previous investigations including gelation with Locust Bean Gum or Konjac Glucomannan (Goycoolea,Richardson, Morris, & Gidley, 1995), viscosity with guar gum (Casas, Mohedano, & García-Ochoa 2000), mechanical and barrier property with gellan gum (Zhang et al., 2020), viscosity with konjac-Mannan and TG (Mirzaei, Alimi, Shokoohi, & Golchoobi, 2018).

- Drug release kinetic: in formulations F_1, F_6, F_7 and F_8 showed the highest regression coefficient in with higuchi model (Table 3). Higuchi model describes the diffusion of API from the matrix and drug delivery system's (DDS) matrix erosion that has been observed repeatedly in XG based DDS (Kar, Mohapatra, Bhanja, Das, & Barik, 2010; Mughal, Iqbal, & Neau 2011; Zambrano-Zaragoza, Quintanar-Guerrero, Del Real, Piñon-Segundo, & Zambrano-Zaragoza, 2017). In this regard, main polymeric component of formulations F_1, F_6& F_7

is XG which strongly navigates the release behavior toward higuchi model. However, F_8 which is totally composed of TG, also was best fitted with higuchi model and describes the release of drug based on Fickian diffusion from insoluble matrix as a square root of time-dependent process which was also discovered in conjugated TG (Dehghan-Niri, Tavakol, Vasheghani-Farahani, & Ganji, 2015; Shafiee, Ahangar, & Saffar, 2019) or combination of TG and XG (Akhtar Rasul et al., 2010).

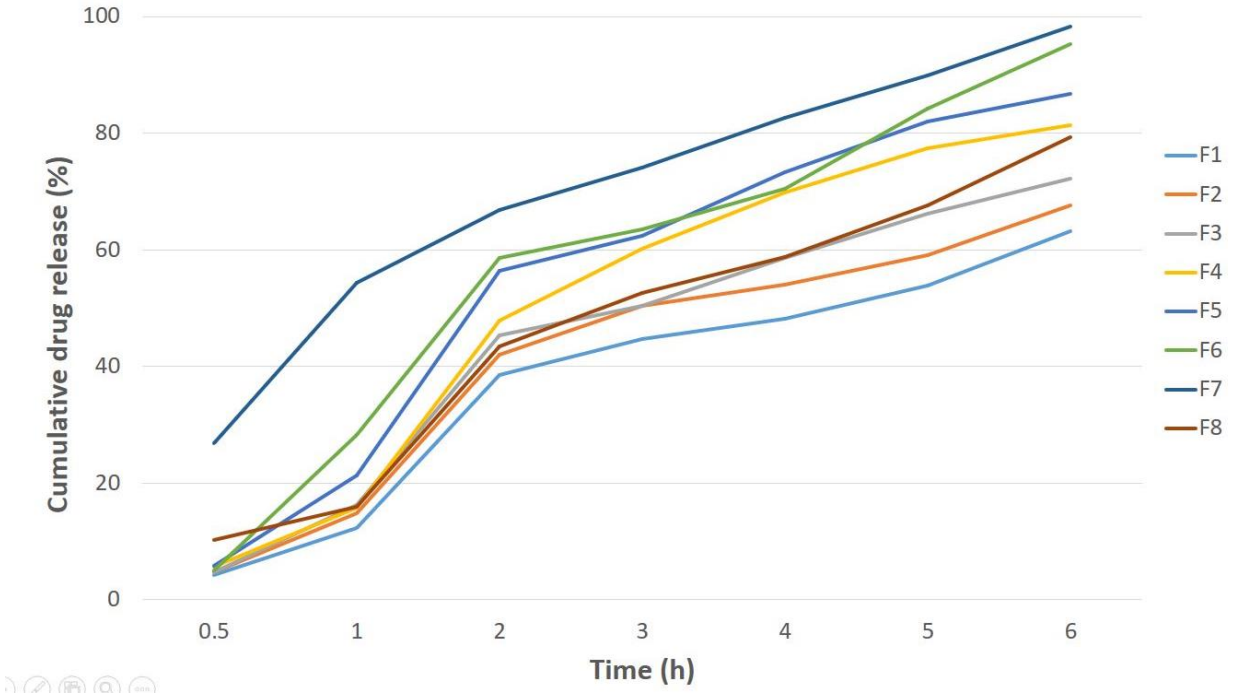

Figure 3. Cumulative drug release of formulations F_1-F_8 vs time.

Table 3. Release kinetic parameters for F_1, F_6, F_7 and F_8 formulations based on mentioned mathematical models.

Formulation	Zero order		First order		Higuchi		Korsemeyer-peppas	
	K_0	R^2	K_1	R^2	K_H	R^2	K_K	R^2
F_1	10.015	0.8935	-0.0702	0.9471	33.028	0.9554	0.2423	0.6588
F_6	14.595	0.9032	-0.2034	0.9103	48.029	0.9617	0.2488	0.5901
F_7	11.098	0.8878	-0.2487	0.8729	36.62	0.9504	0.2325	0.4911
F_8	12.205	0.946	-0.1088	0.9755	39.621	0.9802	0.253	0.6591

Conclusion

Combination of natural polysaccharides provides a tunable platform for development of mucoadhesive DDSs with desirable API release behavior, viscosity, spreadability, mucoadhesion, etc. In this study F1 showed the appropriate physicochemical properties including controlled drug release (63.13% in 6h) with higuchi release model, higher mucoadhesion (77.71 dyne cm-1) and drug content (94.47%) and relatively low spreadability (3.5 cm) which is suitable for local drug delivery. FTIR spectroscopy revealed there is no incompatibility between clotrimazole and natural polymers in formulations.

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