Plant Biotechnology Persa http://pbp.medilam.ac.ir

FORMULATION DESIGN, DEVELOPMENT AND EVALUATION OF QUERCUS INFECTORIA GALLS EXTRACT ORAL GELS FOR ORAL CANDIDIASIS

Fatehalrahman F. Magbool[1], Elamin Ibrahim Elnima[1], Shayoub M. E[1]., Zuheir Osman[1] , Mohammed E. Adam[2] , Elnazeer I. Hamedelniel[3], Abdrhman Mahmoud Gamil[4]

[1]Department of Pharmaceutics and Pharmaceutical Technology, Khartoum University, P.O. Box 1996, Sudan.
[2]Department of Chemistry, Faculty of Pharmacy, University of Khartoum, Khartoum, Sudan.
[3]Associate professor of Pharmaceutics, Faculty of Pharmacy, Omdurman Islamic University – Sudan.
[4]Associate professor of Pharmaceutics, Faculty of Pharmacy, Al-Neelain University – Sudan.

***Correspondence to:**
Dr. Fatehalrahman F. Magbool
fmagbool@yahoo.com

Received: 10 June 2020
Accepted: 26 June 2020
ePublished: : 9 August 2020

Keywords: *Q. infectoria* galls, Anti-Candida activity, Oral gel, Physicochemical properties, Carbopol 940, Xanthan gum

Abstract

The objective of the study is to design, formulate and evaluate an oral gel containing *Quercus infectoria* galls extract for its anti-Candida activity. The gel formulation was designed by using carbopol 940 and xanthan gum as gel forming polymers, propylene glycol, methyl paraben, propyl paraben and required amount of distilled water. The pH was maintained by drop wise addition of Tri-ethanolamine. Eight different gel formulations (F1 to F8) were prepared by dispersion method, using different concentrations of carbopol 940 for carbopol 940-based oral gels (F1and F2), and combined with xanthan gum as secondary gelling polymer for combined polymer-based formulations (F3-F8) have been prepared to study the individual effect of two polymers as well as polymer concentrations, and they were evaluated using official and non-official experiments including organoleptic properties, pH, spreadability, extrudability and viscosity, in vitro release and drug content uniformity. The stability study for the developed gel formulation was done as per ICH guidelines and antifungal activity was evaluated by paper disc diffusion method. The overall pharmaceutical acceptability were satisfactory for the developed oral gels regarding chemical and physical investigations. The viscosity of oral gels was significantly ($P<0.05$) affected by both of polymer concentration and polymer type, also the developed oral gel formulations exhibited antifungal activity against *C. albicans*, it was observed that the biological activity of prepared oral gels significantly ($P=0.03$) increases with decreasing polymers concentration. The accelerated stability testing indicated that all formulations showed a good stability, thus providing a safe and stable gel delivery system. The pharmaceutical evaluations and in vitro results showed that oral gel formulations can be a potential candidate for the delivery of *Q. infectoria* galls ethanolic extract to the oral cavity, with better in vitro characteristics, physicochemical properties and pharmacological activity, using carbopol 940 alone and in combination with xanthan gum as drug carriers.

Citation:
Magbool FF, Elnima EI, Shayoub M. E, Osman Z, Ebied Adam M, Hamedelnie EI, Mahmoud Gamil A. FORMULATION DESIGN, DEVELOPMENT AND EVALUATION OF *QUERCUS INFECTORIA* GALLS EXTRACT ORAL GELS FOR ORAL CANDIDIASIS. Plant Biotechnology Persa. 2020; 2(2): 1-13.

Introduction

Local delivery allows topical treatment of various oral mucosal diseases. However, treatment can be made effective if the drugs can be targeted directly to the site of lesion, thereby reducing the systemic side effects. Oral gel are the semisolid form of drug dosage mainly introduced for the easy dispersion of drug through the mucosa. These drug systems form an intimate contact with the oral mucosal membrane and facilitate the rapid release of drug molecules at the site of absorption [1]. Carbopol 940 is one of the polymeric systems widely used for this purpose, due to its capacity to form gels in aqueous solution, compatibility with many active ingredients, and good patient acceptance [2-5]. Xanthan gum is biocompatible with several gel-forming and non-gel-forming macromolecules and can form a stable gel in conjunction with suitable biopolymer systems. Therefore, xanthan gum has been explored as a potential polymer to form gels [6-9] and as an excipient for tablets in modern medicine [10]. Oral candidiasis is

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[DOI: 10.52547/pbp.2.2.1]

one of the common fungal infections affecting the oral mucosa. These lesions are caused by several Candida spp. among them, *Candida albicans* are commonly seen in the oral cavity. that may be treated with topical and systemic chemotherapeutic antifungal preparations ,these antifungal agents that are available have certain mechanisms of action that are directed towards sterols in the cell membrane or against enzymes those involved in nucleic acid synthesis. As a result of this, these drugs are generally more toxic to humans. *Quercus infectoria* G. Olivier galls; Family – Fagaceae locally known as Ifas are used in folk medicine, and pharmacologically are claimed to have great medicinal value and potential antifungal activity. In this study, a *Q. infectoria* G. Olivier galls was selected because it exhibited a superior potentiality against *C. albicans*.

The aim of the present research work is to explore new alternatives for the treatment of oral candidiasis. Accordingly, the main objectives are to formulate, design and develop a stable, efficacious, and safe local oromucosal drug delivery system of *Quercus infectoria* galls extract.

Materials and Methods

Materials

The galls of *Quercus infectoria* were collected. The plant was identified by a taxonomist at Medicinal and Aromatic Plants Institute, National Center for Research - Khartoum, Sudan.

Chloroform was obtained from (SD Fine India), Glycerol was obtained from (CDH India), Methyl paraben, Propyl paraben, Carbopol 940, Xanthan gum and Triethanolamine was obtained from (SD Fine India), Ethanol was obtained from (National Distillation Company). All other chemicals used were of analytical grade.

Methods

Formulation of *Q. infectoria* galls extract oral gel

Preparation of *Q. infectoria* galls extract

Extraction of *Q. infectoria* galls was carried out according to method descried by Sukhdev. S. H. et at. 2008 [11]. 500 g of the *Q. infectoria* galls was extracted by soaking in 2500 ml 80 % ethanol /and water for about seventy two hours with daily filtration and evaporation.

Physicochemical compatibility of *Q. infectoria* galls extract and gelling polymers as pre-formulation study

Physical compatibility study

Q. infectoria galls extract- excipients blend was taken separately into container and kept for one month study at room temperature and observe the physical changes. After one month storage of *Q. infectoria* galls extract with excipients in various concentrations at room temperature, samples were observed for physical changes such as colour and odour.

Chemical compatibility study

Assessment of possible incompatibilities between the *Q. infectoria* galls extract and different excipients is an important part of pre-formulation. IR measurements were performed using FTIR Spectrophotometer (IR-470; Shimadzu, Japan) by the KBr disc method. The samples were ground, mixed thoroughly with KBr and compressed using IR compression machine and then scanned over the range of 4000 to 400 cm-1. Infrared spectroscopic analysis was done for the powder of *Q. infectoria* galls, polymers (carbopol 940 and xanthan gum), physical mixture of drug and polymers 1:1.

Experimental Design

During formulation two gelling agents were used at different concentrations, resulting in eight different batches of gel bases. In this case for formulations F1and F2, carbopol 940 was used as gelling agent at concentration of 1% and 1.5% w/w respectively. Other formulations F3-F8 containing carbopol 940 and xanthan gum as secondary gelling agent were both used as follows:
a. Carbopol 940 (at concentration 0.5%, 1%, 1.5% and 2% w/w)
b. Xanthan gum (at concentration 0.2% and 0.6% w/w)

A placebo gel was prepared using carbopol 940 and xanthan at concentration 2% and 0.2% w/w respectively. Gel base composition was finalized after doing many trials.

Preparation of *Q. infectoria* galls Extract Oral Gel Formulations

Preparation of Single Polymer Oral Gels

Q. infectoria gall ethanolic extract concentration was 5% w/w in all the prepared formulations. Oral gels were prepared by dissolving an accurately weighed 5.0 gm of *Q. infectoria* gall ethanolic extract powder in 10 gm glycerol using magnetic stirring bar. Glycerol was added as sweetening agent and for its emollient properties. It's also used as dispersant to increase the plasticity, and to decrease the attraction between polymer chains to make them more flexible. Total two gel formulation batches containing only carbopol 940 as gel forming polymer (F1and F2) have been prepared. The calculated amount of water required to prepare 100 gm was added. The specified amounts of the gelling polymer; carbopol 940 (1 & 1.5% w/w), were added slowly to the previously formed mixture under continuous stirring using shear homogenizer. Subsequently, a suitable quantity of triethanolamine was added to the above drug-carbopol 940 solution until gel with appropriate strength and transparency is formed. If required, further triethanolamine is added to adjust the pH of gel near to the pH of oral cavity (5.5-7). Methyl paraben (MP) 0.18% w/w together with propyl paraben (PP) 0.02% w/w, have been added for the preservation of the formulations due to their additive effects with continuous stirring till it got dispersed in the gel to have a homogeneous mixture. Entrapped air bubbles were removed by keeping the gel overnight and also for complete polymer solvation. It was packed in plastic containers with cover and kept in a dark and cool place, with label [12, 13].

Preparation of Combination Polymer Oral Gels

Total six *Q. infectoria* galls extract oral gel formulations (F3-F8) were prepared with various concentrations of carbopol 940 (0.5, 1, 1.5 & 2% w/w) and xanthan gum (0.2 & 0.6% w/w) by the same method previously mentioned, with continuous gentle stirring to avoid air entrapment till a homogenous dispersion was obtained. As per compositions given in table 1.

Pharmaceutical evaluation and quality control

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Table1. Quantitative composition of *Q. infectoria* galls extract polymeric oral gel formulations.

Ingredient /gm	F1	F2	F3	F4	F5	F6	F7	F8	Plain gel
Carbopol	1	1.5	0.5	1	1.5	2	0.5	1	2
Xanthan gum	0	0	0.2	0.2	0.2	0.2	0.6	0.6	0.2
Extract	5	5	5	5	5	5	5	5	0
Methyl paraben	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18
Propyl paraben	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Glycerol	10	10	10	10	10	10	10	10	10
Triethanolamine	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml
Water/ml	To 100	To100	To 100	To 100	To 100	To 100	To 100	To 100	To 100

of prepared *Q. infectoria* galls extract oral gels

The prepared gel formulations were evaluated to study the individual effect of two polymers as well as polymer concentration.

Sensory properties and physical observations

Q. infectoria galls extract oral gel formulations were visually inspected for clarity, color, homogeneity, consistency and presence of particles. In order to investigate the consistency of the formulations, a small quantity of oral gel was pressed between the thumb and the index fingers and the consistency of the oral gel was noticed. Homogeneity: after the oral gels have been set in container, all developed oral gels were tested for homogeneity by visual inspection. They were tested for their appearance and presence of any aggregates. Grittiness: all the formulations were evaluated microscopically for the presence of any appreciable particulate matter which was seen under light microscope. Hence obviously the gel preparation fulfils the requirement of freedom from particular matter and from grittiness [14].

Determination of pH

The pH influences the taste and stability of oral gels. The pH of prepared *Q. infectoria* galls extract oral gels were measured using a digital pH meter (HANN PH 209, Romania) at room temperature 25°C ± 5°C. For this purpose, 0.5 g of oral gel was dispersed in 50 mL of distilled water to make a 1% solution, and the pH of each formulation was done in triplicate and average values are calculated [15, 16].

Measurement of spreadability

The in vitro spreadability check was performed on the prepared *Q. infectoria* galls extract oral gel formulations which can act as an indicator of how will the spread on the oral mucosa surface be when oral gel is applied. Spreading coefficient (Spreadability) was determined by apparatus suggested by Lalit Kumar et.al. 2010 [18].which consists of a wooden block, which was provided by a pulley at one end [17].

Measurement of extrudability

Prepared *Q. infectoria* galls ethanolic extract oral gel formulations were filled in standard capped collapsible aluminum tubes and sealed by crimping to the end. The weight of tubes were recorded and the tubes were placed between two glass slides and were clamped. 500gm was placed over the slides and then the cap was removed. The amount of extruded oral gel was collected and weighed. The percent of extruded oral gel was calculated as; i). When it is greater than 90% then extrudability is excellent. ii) When it is greater than 80% then extrudability is good. iii) When it is 70% then extrudability is fair [19].

Determination of viscosity

The viscosity of different *Q. infectoria* galls ethanolic extract oral gel formulations were determined at room temperature using a HAAKE Viscometer 6 plus (Rotation range / 0.1-200 rpm), using spindle / 3L, and the formulations were rotated at 50 and 100 rotation per minute. Evaluations were done in triplicates and mean ± SD viscosities were calculated [20].

Spectrophotometric studies of *Q. infectoria* galls extract oral gels

i. Estimation of λ max for ethanolic extract of *Quercus infectoria* galls

Estimation was carried out by SHIMADZU-1700 UV spectrophotometer, weigh accurately one gm from the *Q. infectoria* galls extract and dissolve in 30 ml ethanol in volumetric flask 100 ml, shake for 10 min by mechanical means, complete to volume by ethanol, read the absorbance after determining the maximum wave length by scan the same solution in the range 200-400 nm [21, 22].

ii. Preparation and development of standard calibration curve

To construct the calibration curve, *Q. infectoria* galls extract was weighed and a solution of concentration 100 mg/ml was prepared using ethanol and then various dilutions were made, Spectra was run on UV spectrophotometer, and absorbances were noted. A standard calibration curve was developed and used to calculate the concentration of the dug during the study of content uniformity and dissolution study.

Determination of drug content of *Q. infectoria* galls oral gels

Ten mg of *Q. infectoria* galls ethanolic extract oral gel was accurately weighed and dissolved in ethanol in volumetric flask

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100 ml, shake for 10 min by mechanical means, complete to volume by ethanol. The content was filtered through a whatman filter paper. An aliquot of 1ml was pipetted out from filtrate. The extract was estimated spectrophotometrically by using shimadzu UV/VIS spectrophotometer-1700 at 296 nm [22].

Drug release study

Release of *Q. infectoria* galls extract from the prepared oral gel formulations was studied according to USP (1995) [23], by using dissolution Apparatus Calliva Model L-20 UK, using 900 ml of freshly prepared distilled water as a dissolution medium at a temperature of 37°C± 0.5, and the rotation was adjusted at 100 rpm for 45 minutes. Absorbance of aliquots samples of the dissolution medium was read in UV spectrophotometer at λ max 296 nm. The absorbance of 5ml samples of each *Q. infectoria* galls ethanolic extract oral gels were compared with the absorbance of a known concentration of a pure material of *Q. infectoria* galls extract powder, without any additives. The percentages of dissolved amounts were calculated at different time intervals in the dissolution test to determine the rate and extent of release at (5, 10,15, 25, 30 and 45 minutes).

Therapeutic potential and antifungal activity evaluation of prepared *Q. infectoria* galls extract oral gels

The paper disc diffusion method was used to screen the anti-Candidal activity (*Candida albicans* ATCC7596) of prepared *Q. infectoria* galls extract oral gel formulations and performed by using Mueller Hinton agar (MHA). The experiment was carried out according to the National Committee for Clinical Laboratory Standards Guidelines [24]. The diameters (mm) of the inhibition zones were measured, averaged and then the mean±SD values were tabulated. Plane oral gel formulation (without drug) was also tested as a positive growth control result.

Stability study

Q. infectoria galls ethanolic extract oral gel formulations were packed in aluminum collapsible tubes and was placed in stability chamber (LDO-030N/Scott Science, UK), and subjected to accelerated stability studies at 40 °C/75 % RH for a period of three month as per ICH Guidelines [25]. Salt solution of 20gm NaCl was used to obtain relative humidity close to 75%. Samples were withdrawn at one month time intervals and were subjected to evaluation of physical appearance, pH and content uniformity [26].

Statistical analysis

The results were analyzed by SPSS version 24. The mean and SD were obtained and "t" test, One way ANOVA and chi – square test were used for comparison. Data were presented as means ± S.D. Statistical analysis for all the assays results were done using Microsoft Excel program (2016). Linear regression was also used for correlation. P. value was obtained to assess the significance of the results (p value of < 0.05 was considered to be significant).

Results

Q. infectoria galls Extraction Yields

The result indicated that *Q. infectoria* galls have high ethanolic extractive value 15.26 % in comparison to the water 9.24% extractive yield (Table 2). By following the extraction method descried by Sukhdev. S. H et al. 2008 [11], indicates the possibility of considerable amount of polar and non-polar compounds and presence of large quantity of alcoholic soluble constituents.

Table2. *Quercus infectoria* galls ethanol and water extractive values

Solvent	Weight of sample	Weight of extract	Extraction yield %
Ethanol	500 gm	76.3 g	15.26 %
Water	500 gm	46.2 g	9.24 %

Compatibility of *Q. infectoria* galls extract with potential formulation excipients

In this stage of pharmacotechnical development, it is necessary to evaluate the compatibility between drug and excipients. Compatibility study performed between *Q. infectoria* galls ethanolic extract and excipients to assess any compatibility issues which will affect the physiochemical properties of the dosage form which interns alters in-vivo performance of dosage form.

i. Physical compatibility investigation

After 30 days storage of drug extract with excipients at room temperature, samples were observed for physical change but there is no physical change observed in the mixture of extract and polymer combination.

Table3. Physical compatibility investigation of drug extract with excipients at room temperature.

extract /excipients mixture	Parameters			
	physical change after 30 days storage			
	Colour	Odour	Clarity	Homogeneity
Extract+ Carbopol 940	No change	No change	Clear	Homogeneous
Extract+ Xanthan gum	No change	No change	Clear	Homogeneous
Extract+ Carbopol 940 +Xanthan gum	No change	No change	Clear	Homogeneous

ii. Chemical compatibility investigation

Fourier Transform Infra-Red Spectroscopy study was carried out to know any possible interference between the *Q. infectoria* galls extract and excipients. Figure 1; a-e, showed characteristic absorption bands obtained in the *Q. infectoria* galls extract alone and in a mixture of drug with excipients (polymers).

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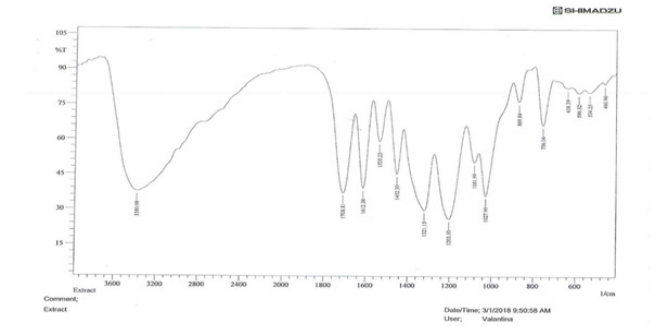
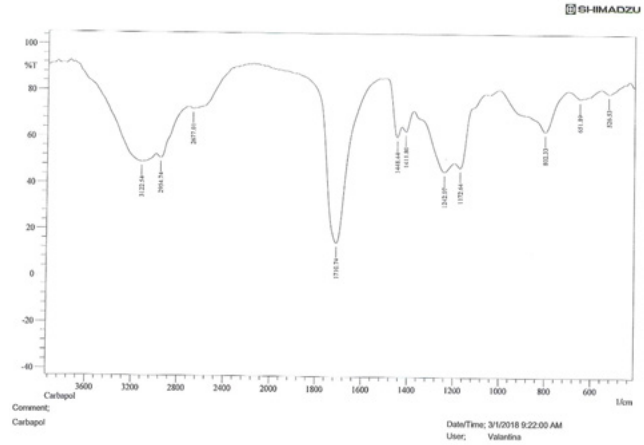


(a)



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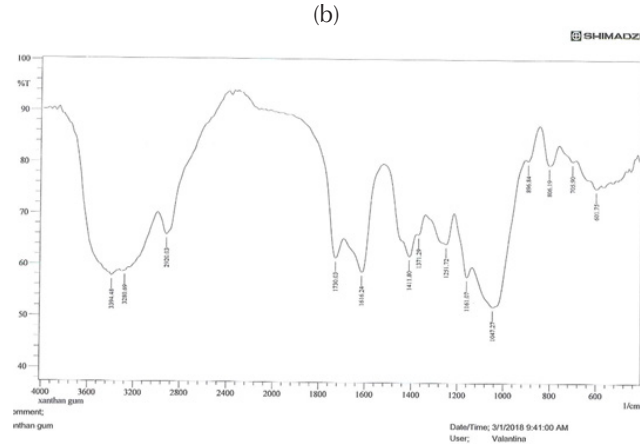

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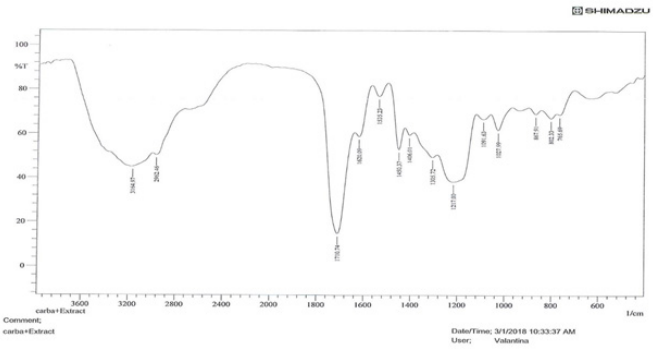

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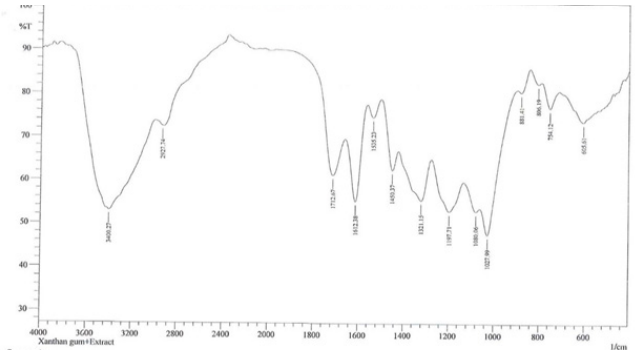

(e)

Figure 1:

FT-IR spectra for the powder of *Q. infectoria* galls, polymers (carbopol 940 and xanthan gum), and physical mixture of drug and polymers 1:1.

a) FT-IR spectra of extract.

b) FT-IR spectra of carbopol 940 polymer.

c)FT-IR spectra of xanthan gum. FT-IR spectra of physical mixture of extract and carbopol 1:1.

d) FT-IR spectra of physical mixture of extract and xanthan gum 1:1.

In light of these findings, the FTIR method, prove that FTIR is a fast screening tool to check compatibility in early stages of a pre-formulation process. With FTIR spectroscopy, it was possible to indicate excipients that may facilitate formulation of the dry extract from *Q. infectoria* galls. Based on these results, all mentioned excipients were found to be compatible with *Q. infectoria* galls ethanolic extract. This study also demonstrates the importance of using instrumental techniques in the early stages of development of herbal medicine, selecting excipients that can optimize the activity of the extract.

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Table 4. Physical appearance and organoleptic properties of *Q. infectoria* galls extract oral gels.

Formulation Code	Texture	Colour	Clarity	Homogeneity	Consistency	Grittiness
Plain	Smooth	white translucent	Clear	Homogeneous	Good	No
F1	Smooth	Light brownish yellow	Clear	Homogeneous	Good	No
F2	Smooth	Light Brownish yellow	Clear	Homogeneous	Good	No
F3	Smooth	Brownish yellow	Clear	Homogeneous	Good	No
F4	Smooth	Brownish yellow	Clear	Homogeneous	Good	No
F5	Smooth	Brownish yellow	Clear	Homogeneous	Good	No
F6	Smooth	Brownish yellow	Clear	Homogeneous	Good	No
F7	Smooth	Brownish yellow	Clear	Homogeneous	Good	No
F8	Smooth	Brownish yellow	Clear	Homogeneous	Good	No

Table 5. pH, Spreadability and extrudability of developed Q, infectoria galls extract oral gels.

Formula Code	pH	Time of Spreading (gm /sec.)(mean± SD, n=3)	P value	Extrudability*
Plain	6.47	21.80± 0.14		good
F1	6.80	1± 0.18		excellent
F2	6.03	0.3± 0.92		excellent
F3	6.29	1.9± 1.75		good
F4	6.33	1.1± 1.38	0.001	excellent
F5	5.94	15.3± 1.57		good
F6	6.50	21.7± 1.57		good
F7	6.47	1.9± 0.7		excellent
F8	5.98	3± 0.26		good

*Mean value of three determinations. Determinations were noted at room temperature, greater than 90% then extrudability is excellent; greater than 80% then extrudability is good; and when it is 70% then extrudability is fair.

Table 6: Viscosity of prepared *Q. infectoria* galls extract oral gels at 50rpm and 100rpm

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Table 6: Viscosity of prepared *Q. infectoria* galls extract oral gels at 50rpm and 100rpm

Formula Code	Polymer composition	Viscosity (mean± SD, n=3)			
		50 rpm	P value	100 rpm	P value
Plain	Carbopol 2%/ Xanthan gum 0.2%	2400± 70.6		1825± 122	
F1	Carbopol 1%	1943± 73.5		1322± 190	
F2	Carbopol 1.5%	3909± 79.8		2712± 273	
F3	Carbopol 0.5%/Xanthan gum 0.2%	2225± 321		1918± 82.1	
F4	Carbopol 1%/Xanthan gum 0.2%	2399± 98.9	0.001	1533± 82.6	0.002
F5	Carbopol 1.5%/Xanthan gum 0.2%	4799± 90.1		2921± 196	
F6	Carbopol 2%/Xanthan gum 0.2%	2335± 79.5		1515± 83.2	
F7	Carbopol 0.5%/Xanthan gum 0.6%	2400± 41.7		1860± 95.2	
F8	Carbopol 1%/Xanthan gum 0.6%	2320± 102		1500± 70.3	

Viscosities were noted at formulation pH and pH 6-7, and at room temperature

Spectrophotometric Studies

λmax of *Quercus infectoria* galls Ethanolic Extract

The UV spectrum of solution of *Q. infectoria* galls extract (100mg/ml) was scanned between 200-400 nm regions on UV spectrophotometer, λmax of *Q. infectoria* galls extract was found to be 296 nm (Figure 2).

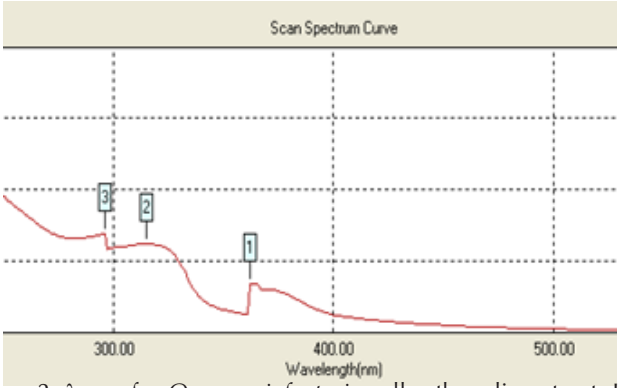

Figure 2: λmax for *Quercus infectoria* galls ethanolic extract, UV spectrum of solution of *Q. infectoria* galls extract (100mg/ml) was scanned between 200-400 nm regions on UV spectrophotometer

Standard Calibration Curve of *Q. infectoria* galls Ethanolic Extract

Scanning studies were carried out in UV region, the method for the estimation for the *Q. infectoria* galls extract showed maximum absorption at wavelength 296 nm (λ max) in ethanol (Figure 2). Standard curve obeyed Beer's law at given concentration range of 0.02 – 0.12 mg/ml (Figure 3) and when subjected to regression analysis, the value of regression coefficient was found to be 0.9988 were as shown in (Figure 3), which showed linear relationship between concentration and absorbance, equation of a straight line as follows:

$$y = ax + b$$

$$y = 6.265x + 0.0423$$

$$R2 = 0.9988$$

Where (y) stands for absorbance and (x) for *Q. infectoria* galls crude extract concentration in the solution. Value of R2, determination coefficient, indicates the precision of the analytical method. This analytical method is considered reproducible when dealing with analysis of different formulae. The maximum absorption showed at wavelength 296 nm. Accordingly, the other different concentrations were calculated from this standard calibration curve.

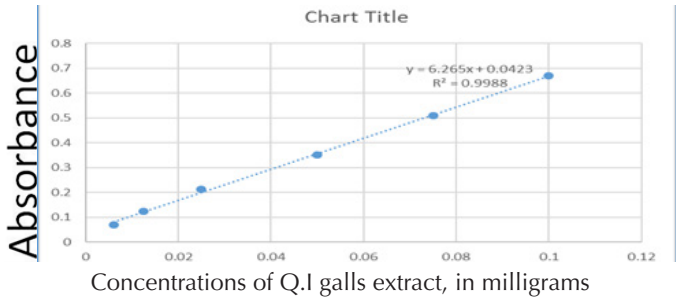

Figure 3: UV-Vis standard calibration curve of *Q. infectoria* galls ethanolic extract,concentrations were calculated [mg/ml] after UV-Vis analyses using this standard calibration curve were calculated from absorbance (A)

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Table 7: Content percentage and release % of *Q. infectoria* galls ethanolic extract developed oral gels: by UV spectrometry at 296nm.

Formulation code	Mean Absorbance*	Content % (mean± SD, n=3)	% Release at 45 min*	Inhibition Zones in mm	P value
Placebo	-	-	-	-	-
F1	0.368	106.36±2.69	93±0.95	10± 2.8 mm	
F2	0.341	98.55±0.98	77.63±2.32	10± 2.4 mm	
F3	0.343	99.13±1.65	94.25±1.65	15± 2.2 mm	
F4	0.339	97.98±0.88	93±1.77	15± 1.4 mm	0.03
F5	0.339	97.98±2.41	92.37±2.95	14± 2.2 mm	
F6	0.339	97.98±2.33	93±1.62	14± 1.8 mm	
F7	0.337	97.40±1.75	93±2.32	15± 1.3 mm	
F8	0.346	100±0.82	93.62±2.86	15± 1.8 mm	

* Mean of three determinations, Standard 0.346

All formulations were found to have drug content in the range of 97.40±1.75% -106.36±2.69%. Therefore, all formulations were within pharmacopeial limit of between 90-110% [23, 27].

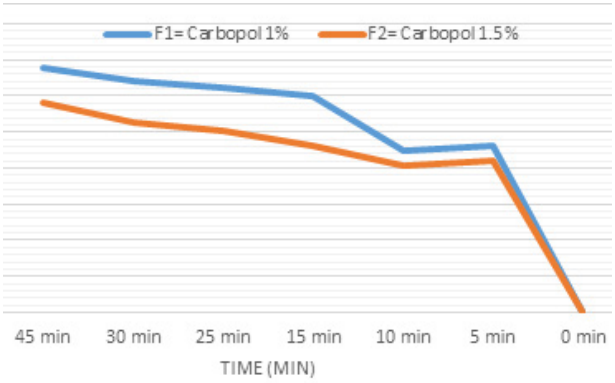

Figure 4: Effect of different concentrations of carbopol 940 on the release of *Q. infectoria* galls extract from the prepared carbopol 940-based oral gels

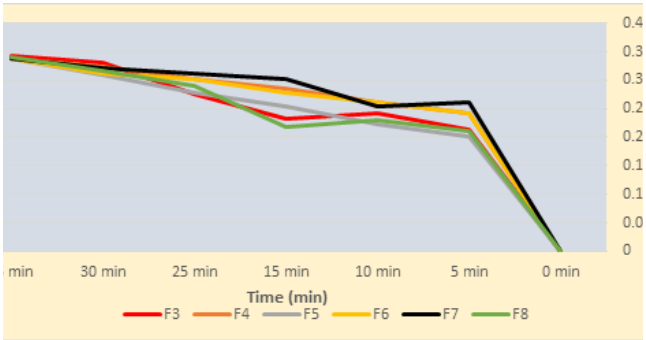

Figure 5: Effect of addition of 0.2 and 0.6% w/w xanthan gum to different concentrations of Carbopol 940 on release of *Q. infectoria* galls extract from the prepared carbopol 940/xanthan gum based-oral gels

Table 8: In vitro antifungal activity of *Q. infectoria* galls ethanolic extract formulated oral gels against Candida albicans.

Formulation code	Extract Concentration %	Polymer/Polymers Composition %	Inhibition Zones in mm	P value
Placebo	-	Carbopol 940 2%/Xanthan 0.2%	-	-
F1	5%	Carbopol 940 1%	10± 2.8 mm	
F2	5%	Carbopol 940 1.5%	10± 2.4 mm	
F3	5%	Carbopol 940 0.5%/Xanthan 0.2%	15± 2.2 mm	
F4	5%	Carbopol 940 1%/Xanthan 0.2%	15± 1.4 mm	0.03
F5	5%	Carbopol 940 1.5%/Xanthan 0.2%	14± 2.2 mm	
F6	5%	Carbopol 940 2%/Xanthan 0.2%	14± 1.8 mm	
F7	5%	Carbopol 940 0.5%/Xanthan 0.6%	15± 1.3 mm	
F8	5%	Carbopol 940 1%/Xanthan 0.6%	15± 1.8 mm	

Key: The diameter of the inhibition zone: < 9 mm, inactive; 9-12 mm, partially active; 13-18 mm, active; >18 mm, very active.

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Table 9: Effects of accelerated stability conditions on physical appearance, pH and content % of developed *Q. infectoria* galls extract prepared oral gel formulations at first month.

Formulation code	Parameters					
	Physical Appearance				pH*	Content%*
	Colour	Odour	Clarity	Homogeneity		
F1	No change	No change	Clear	Homogeneous	6.08	106.35
F2	No change	No change	Clear	Homogeneous	6.01	97.98
F3	No change	No change	Clear	Homogeneous	5.15	95.38
F4	No change	No change	Clear	Homogeneous	6.05	97.10
F5	No change	No change	Clear	Homogeneous	5.80	96.24
F6	No change	No change	Clear	Homogeneous	6.45	97.67
F7	No change	No change	Clear	Homogeneous	6.34	96.24
F8	No change	No change	Clear	Homogeneous	5.91	100

*Average of three determinations
accelerated stability condition at 40°C ± 2°C/75% RH ± 5% RH

Table 10: Effects of accelerated stability conditions on physical appearance, pH and content % of developed *Q. infectoria* galls extract prepared oral gel formulations at 2nd month

Formulation code	Parameters					
	Physical Appearance				pH*	Content%*
	Colour	Odour	Clarity	Homogeneity		
F1	No change	No change	Clear	Homogeneous	5.93	102.30
F2	No change	No change	Clear	Homogeneous	5.52	99.42
F3	No change	No change	Clear	Homogeneous	6.20	98.55
F4	No change	No change	Clear	Homogeneous	5.97	97.10
F5	No change	No change	Clear	Homogeneous	5.79	96.24
F6	No change	No change	Clear	Homogeneous	6.45	97.68
F7	No change	No change	Clear	Homogeneous	6.12	95.38
F8	No change	No change	Not Clear	Homogeneous	5.84	98.27

*Average of three determinations
accelerated stability condition at 40°C ± 2°C/75% RH ± 5% RH

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Table 11: Influences of accelerated stability conditions on physical appearance, pH and content % of prepared *Q. infectoria* galls extract prepared oral gel formulations at 3rd month

Formulation code	Parameters					
	Physical Appearance				pH*	Content%*
	Colour	Odour	Clarity	Homogeneity		
F1	No change	No change	Clear	Homogeneous	5.83	99.42
F2	No change	No change	Clear	Homogeneous	5.83	94.80
F3	No change	No change	Clear	Homogeneous	6.04	96.82
F4	No change	No change	Clear	Homogeneous	6.05	95.08
F5	No change	No change	Clear	Homogeneous	5.98	93.35
F6	No change	No change	Clear	Homogeneous	6.33	97.40
F7	No change	No change	Clear	Homogeneous	6.03	93.06
F8	No change	No change	Not Clear	Homogeneous	5.83	97.69

*Average of three determinations
accelerated stability condition at 40°C ± 2°C/75% RH ± 5% RH

Discussion

The oral gels were assessed for its sensory characteristics and qualities, from the presented results given in (Table 4), the oral gel formulations had a smooth texture, good consistency, clear, free from particles and homogeneous it was concluded that all the formulated oral gels showed overall good physical appearance. The colour of the oral gels was light brownish yellow for F1and F2, whereas formulations F3-F8 brownish yellow in colour (Table 4), which were the appearance they got from the nature of the polymer/polymers used. Most likely, as already known, the polymer nature and it is concentration greatly impact the gel texture. Regardless the polymer/polymers presence and concentrations, there was no changes in other physical characteristics were observed between prepared oral gels. The present study showed no significant difference in consistency and homogeneity when comparing different type and different polymer concentrations. F1 and F2 had an advantage of providing an excellence appearance without having a negative impact on homogeneity and consistency.

Effects of polymer type and polymer concentration on pH

The salivary pH ranges from 5.5 to 7 [28, 29], the pH values of the prepared medicated oral gels were found to be in the range from 5.94 to 6.80 (Table 5), It was found that pH values of all formulations including placebo formula, where in this range indicating the incorporation of extract have not negative impact on the pH, and thereby not causing any damage to the hard and soft oral tissues. Thus, it may be assumed that these formulations are applicable for oral mucosal and can be used without the risk of irritancy. From the results, it is obvious that, the combination of carbopol 940 with xanthan gum had no significant effect on the pH, whereas a successive reduction of pH was observed with increased carbopol 940 concentration, which is attributed to the acidic nature of the polymer.

Effects of polymer type and polymer concentration on spreadability and extrudability

The delivery of the correct dose of the drug depends highly on the spreadability of the formulation, therefore, the therapeutic efficiency of a formulation depends on its spreading value. The spreadability of *Q. infectoria* galls extract oral gel formulations following the spreadability test were found to range from 0.3±0.92 gm /sec. to 21.7±1.57 gm/sec. (Table 5), which are considered acceptable to avoid improper distribution of active drug. Formulations with low polymer concentrations, showed the highest spreadability value (Table 5). In this study the spreadability of the prepared oral gels was significantly (P=0.001) decreased as the polymers concentration increased (Table 5), this is due to the fact that an increase in polymer concentration increases the repulsion between chains, increases the cross linking between chains, and reduces the spreadability [30]. It also observed that moderate negative correlation between speradability values of oral gels and polymers concentration (correlation = - 0.3; P=0.02).

It is clear from the results of extrudability measurement, oral gel formulations possess satisfactory extrudability values, and all of gelling agents provided the significant contribution to extrudability properties of developed oral gels (Table 5). It was observed that the extrudability tend to reduce upon increase in the concentration of polymers.

From the results the viscosities (Table 6) of the prepared oral gels was significantly ($p<0.05$) affected by polymer type and it was found in the following order: carbopol 940> carbopol 940/ xanthan gum combination found in (F1and F2) and (F3 – F8) respectively as shown in table 5. The behavior of formulations varied with the polymer concentration, it was observed that increasing polymer concentration led to a significant ($p<0.05$) increase in oral gel viscosity. The study also showed positive correlation between viscosity values at 50 rpm of oral gels and polymers concentrations (correlation = 0.1; P=0.05), and showed positive correlation between viscosity values at 100 rpm of oral gels and polymers concentrations (correlation = 0.2; P=0.04). The use of

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xanthan gum as secondary thickening agent have no descriptive variation on the viscosity of the formulations. Carbopol 940 use at 0.5% to 2% in the oral gel formulations showed descriptive results on the viscosity and physicochemical properties, it was seen to be more contribute to the viscosity behavior of formulations. So, the formulations should have an optimum viscosity for easy and good efficiency on mucosal application.

Drug content was one of a significant requirement for any type of dosage form. Amount of the drug present in the formulation should not deviate beyond certain specified limits from the labeled amount. All formulations were found to having drug content in the range of 97.40±1.75%-106.36±2.69%, were within desired range of 90% to 110% [27] (Table 7), representing homogenous drug distribution throughout gels. This indicate that process employed to prepare oral gels in this study was capable of producing gels with uniform drug content and minimal gel variability. Concentration of gel formers and polymer type have shown no profound effect on *Q. infectoria* galls extract content of gel formulation batches. We can conclude that uniform drug loading of *Q. infectoria* galls extract was found in these oral gel formulations in spite different type and concentrations of gel forming polymer used for developing these different oral gel bases.

The percent of *Q. infectoria* galls ethanolic extract released over a period of 45 minutes from the prepared oral gel formulations containing the same initial drug concentration of 5% w/w are discussed according to two variables; different polymer concentrations and different polymer type.

From the results, it is observed that the release of *Q. infectoria* galls extract from the prepared oral gel formulations decrease as an inverse function of polymer concentrations. For carbopol 940-based formulations the release of *Q. infectoria* gall extract from carbopol 940 based oral gels were inversely related with the polymer concentrations, it was observed that the percentage of drug released in dissolution medium showed extremely significant difference (P=0.04) when the carbopol 940 concentration is varied (Figure 4). These findings are in agreement with the data obtained by Songkro. et al. [31]. On the other hand, these findings are in disagreement with the results reported by Macedo. et al. [32], they stated that increasing carbopol 940concentration from 1 % to 2 % w/w had no significant effect on tolmetin release from gel formulations. Initial release of the drug is significantly affected (P=0.04) by the concentration of gelling agent/s in all cases (Tables 7). Several literatures agree with our results like that findings of Lubna A. et al. [33].

In vitro release studies were also performed to investigate the effect of polymer type on release performance of the developed oral gel formulations. From the results, they found a significant difference in *Q. infectoria* galls extract release from carbopol 940-based formulations and carbopol 940/xanthan gum combination polymer-based oral gels indicating that the drug release is influenced by the nature of each individual polymer, it was observed that the amount of drug released was influenced by the type of polymer base used (Figure 5) but statistically non-significant (P>0.05), and it was found in the following order carbopol 940/xanthan gum combination > carbopol 940 based oral gels, this may be due to the higher viscosity of carbopol 940 compared with carbopol 940/xanthan polymer combination based gels which was responsible for hindering drug release from gel matrix. It is obviously clear from the previous results that the prepared *Q. infectoria* galls extract oral gel formulations using carbopol 940/xanthan gum combined polymers at different concentrations showed an acceptable drug release (Table 7), The results showed that the release profiles of the six formulations were found to be nearly similar, 93.62±2.86%, 93±0.95%, 93±1.77%, 93±1.62%, 93±2.32%, 92.37±2.95%, for F8, F1, F4, F6, F7, and F5 respectively (Table 7). The similarity of drug release profiles from formulations containing different concentrations of carbopol 940/xanthan gum polymers were an unexpected, these results might be attributed to the fact that, formulations may have same degree of dissolution-diffusion mechanism through the gel, and also may have same degree of polymer disintegration and consequently same rate of drug release, and also may attributed to addition of xanthan gum as secondary gelling agent may modify the viscosity of the system. Whereas the highest release was shown by formulation F3 of 94.25±1.65%. Finally, the results of the in-vitro release study verified that the concentration of polymer had a remarkable influence on the drug releasing from the gels [34].

In this study, all developed oral gel formulations containing extract at a concentration of 5% w/w exhibited antifungal activity against *C. albicans* with a clear zone diameter of 10± 2.4 mm to 15± 2.2 mm (Table 8). Plain gel formulation (without drug) was also tested as a positive growth control result, It was observed that the placebo (control) did not possess any activity to inhibit the growth of *C. albicans*, which strengthens the result obtained for the developed gels that the activity was merely from the plant extract, and also all the excipients were devoid of any pharmacological activity we can confirm that the obtained results are due the active principles in the herbal formulations. From the in vitro antifungal activity of carbopol 940-based oral gels (F1 and F2), it was found that *Candida albicans* is less susceptible with inhibition zones of 10± 2.8 and 10± 2.4 mm respectively, than that shown in the prepared oral gels using combination of CP 940 and XG at different concentrations, they exhibited a good inhibition zones; 15 ± 2.2 mm, 15± 1.8 mm, 15± 1.4 mm, 15± 1.3 mm, 14± 2.2 mm, 14± 1.8 mm for F3, F8, F4, F7, F5 and F6 respectively, against *Candida albicans*, indicating that polymer type have shown profound effect on the antimicrobial effectiveness of the prepared *Q. infectoria* galls extract gel formulation batches.F3 containing lower carbopol 940/xanthan gum concentration possess highest activity against *C. albicans* (Table 8), it was observed that the biological activity of prepared oral gels significantly (P=0.03) increases with decreasing polymers concentration, this may due to high release rate and lower viscosity of the gel. In this study the biological activity of developed *Q. infectoria* galls extract oral gels was correlated negatively (correlation = - 0.5) with polymer/s concentration, the study showed that the anti-candida activity of *Q. infectoria* galls extract oral gels decreased significantly (P=0.03) with increasing polymer/s concentrations, this may be due to high viscosity of gels negatively affects the release of active ingredients from gels [35].

The prepared formulations were subjected to observation of some parameters like Physical appearance, pH and content uniformity during the stability studies [26]. The findings presented in the current study indicate that all formulations showed a good stability, thus providing a safe and stable gel delivery system. The formulation and subsequent evaluation of the gels presented here showed no phase separation and the formulations were stable in appearance. There was no change in its colour, odour, clarity, ho-

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mogeneity and overall physical appearances (Tables 9-11). It can be concluded that the *Q. infectoria* galls extract oral gels were physically and chemically stable at 40°C ± 2°C/75% RH ± 5% RH for a period of 3 months.

Conclusion

It can be concluded that proper selection of polymers and drug is a prerequisite for designing and developing a local oro-mucosal drug delivery. The pharmaceutical evaluations and in vitro results showed that oral gel formulations can be a potential candidate for the delivery of *Q. infectoria* galls ethanolic extract to the oral cavity, with better in vitro characteristics, physicochemical properties and pharmacological activity, using carbopol 940 alone and in combination with xanthan gum as drug carriers.

Acknowledgment

The authors are thankful to Medicinal and Aromatic Plants Institute, National Center for Research and department of Pharmaceutics University of Khartoum- Khartoum, Sudan.

Authors' contribution

The manuscript was carried out, written, and approved in collaboration with all authors.

Conflict of interests

All authors declare that no conflict of interest exist.

Funding/Support

Department of Pharmaceutics University of Khartoum-Khartoum, Sudan.

Medicinal and Aromatic Plants Institute, National Center for Research

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