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DESIGN, FORMULATION, AND EVALUATION OF CARBOPOL 940 AND XANTHAN GUM AS GEL BASES FOR ORAL LOCAL DRUG DELIVERY FOR ORAL MUCOSAL INFECTIOUS DISEASES

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ABSTRACT
Local drug delivery systems have been used for a long time; in particular, for the local therapy of diseases affecting the oral cavity. Oral mucosa diseases are among the most common diseases affecting humans, and they can be effectively treated by topical therapeutic approaches. Infectious agents targeting the oral mucosa include viral, fungal and bacterial species. Local drug delivery can provide a more targeted and efficient drug-delivery option than systemic delivery for diseases of the oral mucosa. Oromucosal gels are semi-solid preparations containing one or more active substances intended for administration to the oral cavity and/or the throat to obtain a local or systemic effect. Oral gels should have acceptable physical and chemical parameters and should also be stable over the period of use. The objectives of this study were to design, develop oromucosal gel base formulations for oral local drug delivery for oral mucosal infectious diseases, and optimization of different oral gel bases through pharmaceutical characterization including evaluation of sensory and organoleptic properties as well as physicochemical characteristics.

KEYWORDS: Oromucosal gels, carbopol 940, xanthan gum, physicochemical properties, viscosity, sensory and organoleptic properties.

Different gel formulations were prepared using carbopol 940 and xanthan gum, the other additives used are triethanolamine was used in the formulations as a buffering system, methyl paraben (0.18% w/w) together with propyl paraben (0.02% w/w) have been used for the preservation of the formulations due to their additive effects. Glycerol was used as sweetening agent and for it is emollient properties. Therefore formulation factors affecting the physical appearance and physicochemical properties and performance of prepared oral gel bases were studied, particularly the effects of different polymer types, as well as itis different concentrations. The present study showed no significant difference in consistency and homogeneity when comparing different type and different polymer concentrations. It was found that pH values of all formulations where in the range and thereby not causing any damage to the hard and soft oral tissues. It is obvious that, the combination of carbopol 940 and 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. In this study the viscosity of the prepared oral gels was significantly (P<0.05) affected by polymer type. It was observed that increasing polymer concentration led to a significant (P=0.02) increase in gel viscosity, the study shows positive correlation between viscosity values at 50 rpm of oral gels and polymers concentrations (correlation = 0.1; P = 0.05), and also shows positive correlation between viscosity values at 100 rpm of oral gel bases and polymers concentrations (correlation = 0.2; P = 0.04). In this study the spreadability of the prepared gel bases was significantly (P = 0.002) decreased as the polymer concentration increased, increasing carbopol 940 concentration significantly (P<0.05) reduce spreadability of formulas. It also observed that moderate negative correlation between speradability values of oral gel bases and polymers concentrations (correlation = - 0.3; P = 0.02). All of gelling agent provided the significant contribution to extrudability properties of oral gels. It was observed that the extrudability tend to reduce upon increase in the concentration of polymers. F1 and F4 gel

formulations were selected as an optimum formulas since it have good spreading behaviour and excellent extrudability, in addition to pH value of 6.80 and 6.33 for F1 and F4 respectively, which is within the range of healthy oral cavity. Additionally F1 and F4 have an acceptable physical and sensory properties, homogeneity, consistency and viscosity, but F1 had an advantage of providing an transparent appearance without having a negative impact on homogeneity and consistency. The presented work envisages the feasibility of the use of the carbopol 940 as gelling agent and in combination with xanthan gum at different concentrations as good oral gel bases for local oral drug delivery system for local oromucosal infectious diseases. As expected, the natural and synthetic polymers form a better formulations. This study suggests variable concentrations of gelling agents as vehicles for oromucosal gels. Hence, it gives the formulator more options other than the limited available gels used frequently as oral gels. In this contribution, we developed and evaluated the oral gel bases with the different concentrations of carbopol 940 and xanthan gum to obtain the optimized Formulations which is suited for application as an local oral gel delivery system of drugs for treatment of local oromucosal diseases.

INTRODUCTION

Modern pharmaceutical science has provided us with a wide range of substances to be administered with a wide large variety of dosage forms. Local drug delivery systems have been used for a long time; in particular, for the local therapy of diseases affecting the oral cavity. Although these diseases are often extremely responsive to local therapy, the mouth often presents various difficulties in the application of topical compounds (owing to saliva and the mouth's different functions), resulting in a short retention time of dosage forms with a consequent low therapeutic efficacy. Development of novel drug delivery techniques that minimize toxicity and improve efficacy offers prospective benefits to patients. Oral mucosa diseases are among the most common diseases affecting humans, and they can be effectively treated by topical therapeutic approaches.

Oral route has been the most convenient and commonly employed route of drug delivery. Oral mucosal drug delivery is an alternative and promising method of systemic drug delivery which offers several advantages. 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. There are very few topical formulations that have been designed specifically for oral mucosal diseases. Most topical therapies currently used by oral medicine specialists for treating oral mucosal diseases are those used in the treatment of dermatological conditions. As such, they have not been designed to be used in an aqueous environment constantly bathed in saliva, which may cause much of the drug to be washed off and lost. Repeated dosing is also required to obtain a therapeutic dose. Delivery systems designed specifically for the oral mucosa capable of sustained release would be beneficial in the treatment of many oral diseases.

Local drug delivery can provide a more targeted and efficient drug-delivery option than systemic delivery for diseases of the oral mucosa. The main advantages of local drug delivery include (i) reduced systemic side effects, (ii) more efficient delivery as a smaller amount of drug is wasted or lost elsewhere in the body, (iii) targeted delivery as drugs can be targeted to the diseased site more easily when delivered locally, thereby reducing side effects. Furthermore, many oral diseases are chronic and, hence, require chronic treatment regimens. In addition, most oral diseases can be treated locally, without the need for ingestion and the systemic distribution of drugs. Thus, local drug delivery provides a more targeted delivery, as smaller amounts of drug can be easily targeted at the site of the disease, thereby reducing side effects; however, the oral mucosa has a small surface area and limited exposure times.[1]

Infectious agents targeting the oral mucosa include viral, fungal and bacterial species. The diversity and scope of these infections were recently reviewed.[2,4] Host exposure to infectious agents, changes in the oral environment, interactions with the oral microbiome and reduced host defenses all potentially contribute to development of opportunistic and non-opportunistic infections of the oral mucosa. Topical and locally delivered antibiotics and antiseptics for the oral and periodontal diseases, such as chlorhexidine, tetracycline, doxicycline, minocycline and metronidazole, have been reviewed elsewhere.[5]

Antifungal drugs are commonly delivered topically to the oral mucosa to treat oral candidiasis.[6] The most commonly used formulations include topical nystatin, clotrimazole, miconazole and itraconazole. Currently, there are no effective topical treatments available for intra-oral infections caused by the human herpes viruses or the human papilloma viruses or picornaviruses. Antiviral topical therapies (5% acyclovir cream, 1% penciclovir cream, 10% docosanol cream and 3% foscarnet cream) are available for recurrent labial herpes[7] and some providers have used dermatologic antiviral or sclerosing preparations in the mouth.

Advances in prevention and management of oral mucosal infections will require new agents and improved mechanisms of topical drug delivery. A phase III randomized clinical trial of a diluted 0.00165% topical gentian violet mouth rinse[8] compared with nystatin mouth rinse to treat oral candidiasis associated with human immunodeficiency virus is currently being conducted by international investigators in the U.S. AIDS Clinical Trials Network. Use of probiotics delivered by lozenges or in chewing gum has been suggested for altering oral infectious disease susceptibility (primarily to dental caries and

periodontitis, but to a lesser extent oral fungal infections) via intermicrobial species interactions and induction of immuno-stimulatory effects.[9] Antiviral and antifungal pharmacokinetics need to be altered to allow targeted delivery, rapidly followed by sustained release and prolonged retention of high drug concentration localized at the oral infection site. To enhance the bioavailability and therapeutic efficacy of existing azole antifungals, new drug delivery strategies and drug formulations are needed to improve the aqueous wetting and dissolution properties of azole antifungals by increasing their chemical potential, stabilizing the drug-delivery system and targeting high concentration of the azoles to the infection sites.[10] A mucoadhesive buccal slow-release tablet formulation containing 50 mg of miconazole applied once daily to treat pseudomembranous candidiasis has shown efficacy and reduces the need for the repeated applications associated with conventional topical antifungal agents.[11] A similar product containing acyclovir has been developed and is in phase III clinical trials for once daily local treatment for recurrent herpes labialis. An occlusive hydrocolloid patch, devoid of any medication has shown similar efficacy to topical acyclovir in the management of herpes labialis.[12] Many researchers and investigators have reported the effectiveness of delivering various drugs through the oral mucosa using different preparations. Gels are semisolid systems in which a liquid phase is constrained within a three-dimensional polymeric matrix (consisting of natural or synthetic polymers) in which a high degree of physical (or sometimes chemical) cross-linking has been introduced. The term "Gel" was introduced in the late 1800 to name some semisolid material according to pharmacological, rather than molecular criteria. The U.S.P. defines gels as a semisolid system consisting of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid. A number of polymers are used to provide the structural network that is the essence of a gel system. These include natural gums, cellulose derivatives, and carbomers.

Oromucosal gels are semi-solid preparations containing one or more active substances intended for administration to the oral cavity and/or the throat to obtain a local or systemic effect.[13] Preparations intended for a local effect may be designed for application to a specific site within the oral cavity such as the gums (gingival preparations) or the throat (oropharyngeal preparations). Preparations intended for a systemic effect are designed to be absorbed primarily at one or more sites on the oral mucosa. For many oromucosal preparations, it is likely that some proportion of the active substance(s) will be swallowed and may be absorbed via the gastrointestinal tract. Oromucosal preparations may contain suitable antimicrobial preservatives and other excipients such as dispersing, suspending, thickening, emulsifying, buffering, wetting, solubilising, stabilising, flavouring and sweetening agents.[13] Oral gels should have acceptable physical and chemical parameters and should also be stable over the period of use. These parameters include the viscosity, pH, spreadability, antimicrobial activity etc, under the suitable storage conditions.

Carbopol 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.[14,17] It can be used without supplementary stabilization, or after neutralization with TEA (tri ethanolamine). TEA neutralizes the carboxylic groups of the polymer and facilitates the formation of cross-links between the polymeric chains. Many works were reported on these systems.[18,20] Neutralization of the polymer carboxylate groups using an alkaline substance makes them highly ionized to form rigid gels.[21,24] This neutralization step is considered as the most common way to can be accomplished by adding a common base, like sodium hydroxide or organic amines, such as triethanolamine, which cause the carboxylate groups of these polymers to be converted into a ionization of these carboxylate groups on the polymer backbone, electrostatic repulsion amongst the negatively charged particles is observed which finally adds to the swelling and thickening capabilities of these polymers.[15]

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[25,28] and as an excipient for tablets in modern medicine.[29] It has also been shown by several authors that xanthan gum can play a successful role in matrix formulations for oral controlled-release drug delivery.[29,30] Moreover, it has been proven that, as a candidate for hydrophilic matrix formulations, xanthan gum has some economical as well as pharmaceutical superiority over most other water-soluble biopolymers.[31] A shear-thinning flow behavior of xanthan gum allows easy extrusion from the tube or from the pump dispenser. Xanthan gum is soluble in both cold and hot water. Like most other hydrocolloids.

Therefore, the current work is aimed to design an oral gel bases containing carbopol 940 alone and carbopol 940 /xanthan gum combination polymers at different concentrations as Oromucosal gel delivery system od drugs for local oral mucosa diseases, and optimization of different oral gel bases through pharmaceutical characterization including evaluation of sensory and organoleptic properties as well as physicochemical characteristics.

MATERIALS AND METHODS

Carbopol 940, xanthan gum, triethanolamine, methyl paraben, propyl paraben and glycerol were obtained from CDH – India.

Experimental Design

During formulation two gelling agents used at different concentrations, resulting in eight different batches of oral gel bases. In this case formulations F1and F2 Carbopol 940 was used as gelling agent at concentration of 1% and 1.5% respectively, other formulations F3-F8 containing Carbopol 940 and Xanthan as secondary gelling agent, the two gelling agents were used as follows:

a. Carbopol 940 (at concentration 0.5%, 1%, 1.5% and 2%)

b. Xanthan gum (at concentration 0.2% and 0.6%)

Gel base composition was finalized after doing many trial and errors.

Preparation of Gel Bases[32,33]

a. Preparation of single polymer oral gel

Parabens were dissolved in 8.3g distilled water using ultrasound apparatus at 55°C, glycerol were added slowly under continuous stirring, the required quantity of carbopol 940 was weighed and was slowly sprinkled to the previous solution under continuous stirring using shear homogenizer. 0.5 ml of TEA was added to carbopol 940 dispersion with continuous stirring till transparent clear gel was formed. The resultant gel masses were left over night at room temperature for complete swelling.

b. Preparation of combination polymer gel

Different oral gel formulations were prepared with various concentrations of carbopol 940 and xanthan gum by the same method mentioned previously, with continuous gentle stirring to avoid air entrapment till a homogenous dispersion was obtained. Different formulations of prepared oral gel are given in (Table 1).

Optimization of Developed Oral Gel Base Formulations

Various trials were required for the complete optimization of oral gel bases; and these trials were based on:

a) Optimization of Manufacturing Processes

b) Optimization of Formulation

Optimization Studies Included Assessment of The

i) Effects of polymer type and polymer concentrations on Sensory properties and physical appearance of oral gel base formulations.

ii) Influence of polymer type and polymer concentrations on physicochemical properties of oral gel base formulations.

Pharmaceutical Evaluation of Oral Gel Base Formulations

i. Sensory properties and physical observation of oral gel formulations

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 gel was pressed between the thumb and the index fingers and the consistency of the gel was noticed.

Homogeneity: After the gels have been set in container, all developed 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 form grittiness.[34]

ii. Determination of pH[35,36]

The pH influences the taste and stability of oral gels. The pH of prepared oral gel bases was 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 base 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.

iii. Spreadability[37]

The in vitro spreadability check was performed on oral gel base formulations which can act as an indicator how is the spread on the mucosa surface when applied. Spreadability was determined by the apparatus which consists of a wooden block, which was provided by a pulley at one end. By this method spreadability was measured on the basis on slip and drag characteristics of gels. An excess of gel base (about 2 gm) under study was placed on this ground slide. The gel was then sandwiched between this slide and another glass slide having the dimension of fixed ground slide and provided with the hook. A one kg weighted was placed on the top of the two slides for 5 min. to expel air and to provide a uniform film of the gel between the slides. Excess of the gel was scrapped off from the edges. The top plate was then subjected to pull of 80 gm. With the help of string attached to the hook and the time (in sec.) required by the top slide to cover a distance of 7.5 cm be noted. A shorter interval indicates better spreadability. Spreadability was calculated using the following formula:

$S = M \times L / T$

Where, S= Spreadability,

M= weight in the pan (tied to upper slide),

L= Length moved by the slide,

T= Time (in sec.)

iv. Extrudabilty[38]

The oral gel base 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 gel

base was collected and weighed. The percent of extruded oral gel base 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.

v. Determination of Viscosity

The viscosity of different oral gel base formulations was determined at room temperature using a HAAKE Viscometer 6plus (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 viscosities were calculated.[39]

Statistical analysis

Finally the result were analyzed by SPSS version 24. The mean and SD were obtained and "t" test, One way ANOVA and chi – square test used for comparison. Linear regression was also use for correlation. *P*. value was obtained to assess the significance of the results (*p* value of < 0.05 was considered to be significant).

RESULTS

Table 1: 100 gm formula for preparation of oral gel base systems.

Ingredient /Gm	F1	F2	F3	F4	F5	F6	F7	F8
Carbopol	1	1.5	0.5	1	1.5	2	0.5	1
Xanthan gum	0	0	0.2	0.2	0.2	0.2	0.6	0.6
Methyl parapen	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18
Propyl parapen	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Glycerol	3	3	10	10	10	10	10	10
Triethanolamine	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml
Water/ml	To 100	To 100	To 100	To 100	To 100	To 100	To 100	To 100

Table 2: Physical appearance of formulated gel bases.

Formulation Code	Texture	Colour	Clarity	Homogeneity	Consistency	Grittiness
F1	Smooth	Transparent	Clear	Homogeneous	Good	No
F2	Smooth	Transparent	Clear	Homogeneous	Good	No
F3	Smooth	white translucent	Clear	Homogeneous	Good	No
F4	Smooth	white translucent	Clear	Homogeneous	Good	No
F5	Smooth	white translucent	Clear	Homogeneous	Good	No
F6	Smooth	white translucent	Clear	Homogeneous	Good	No
F7	Smooth	white translucent	Clear	Homogeneous	Good	No
F8	Smooth	white translucent	Clear	Homogeneous	Good	No

Table 3: Physicochemical properties of prepared oral gel bases.

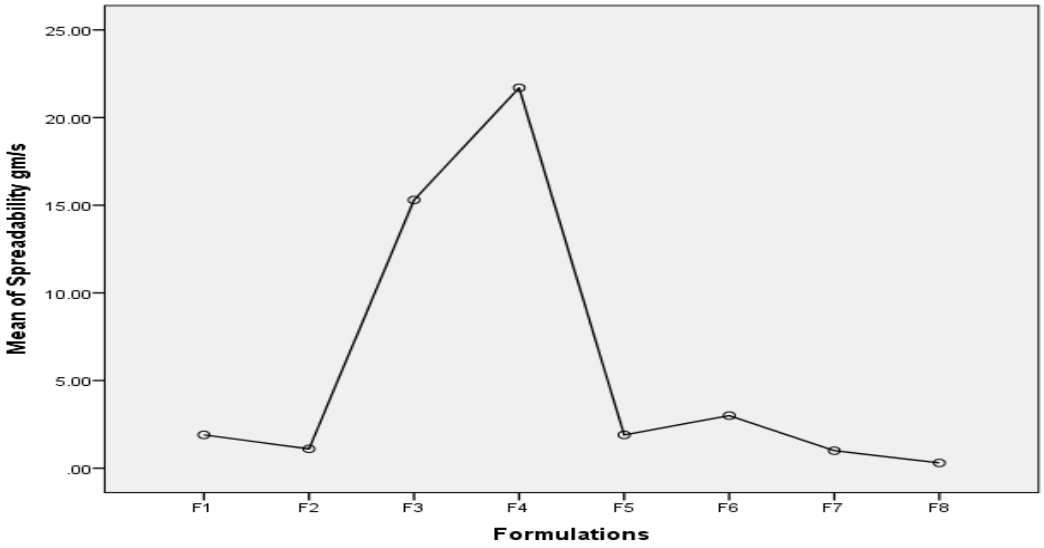
Formula Code	pH*	Time of Spreading (gm /sec.) (mean± SD, n=3)	*P* value	Extrudability*
F1	6.80	1± 0.18	0.001	excellent
F2	6.03	0.3± 0.92		excellent
F3	6.29	1.9± 1.75		good
F4	6.33	1.1± 1.38		excellent
F5	5.94	15.3± 1.57		good
F6	6.50	21.7± 1.57		good
F7	6.44	1.9± 0.7		excellent
F8	5.98	3± 0.26		good

*Mean value of three determinations.

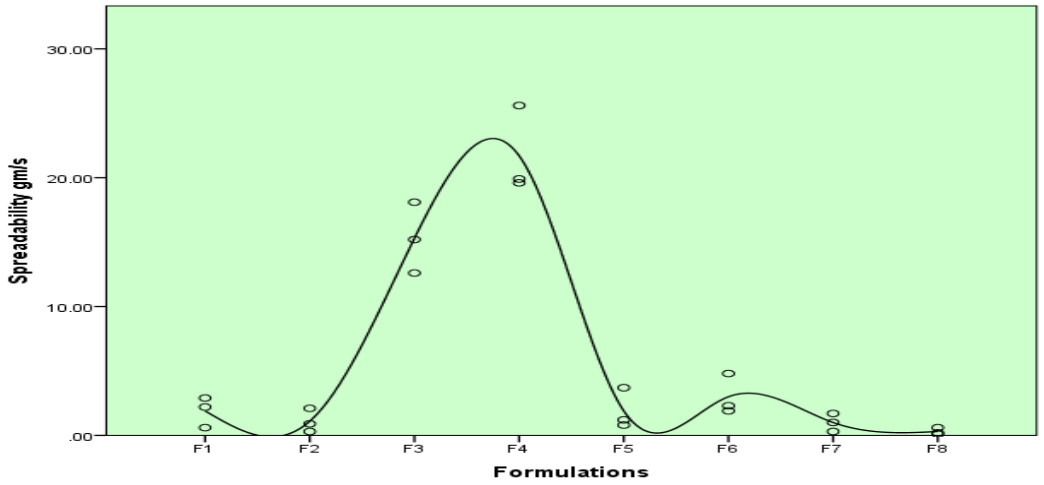
Table 4: Viscosity of developed oral gel bases at 50rpm and 100rpm.

Formula Code	Polymer composition	Viscosity (mean± SD, n=3)			
		50 rpm	P value	100 rpm	P value
F1	Carbopol 1%	1943± 73.5	0.001	1322± 190	0.002
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		1533± 82.6	
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 of all the formulations were noted at formulation pH and pH 6-7, and at room temperature.

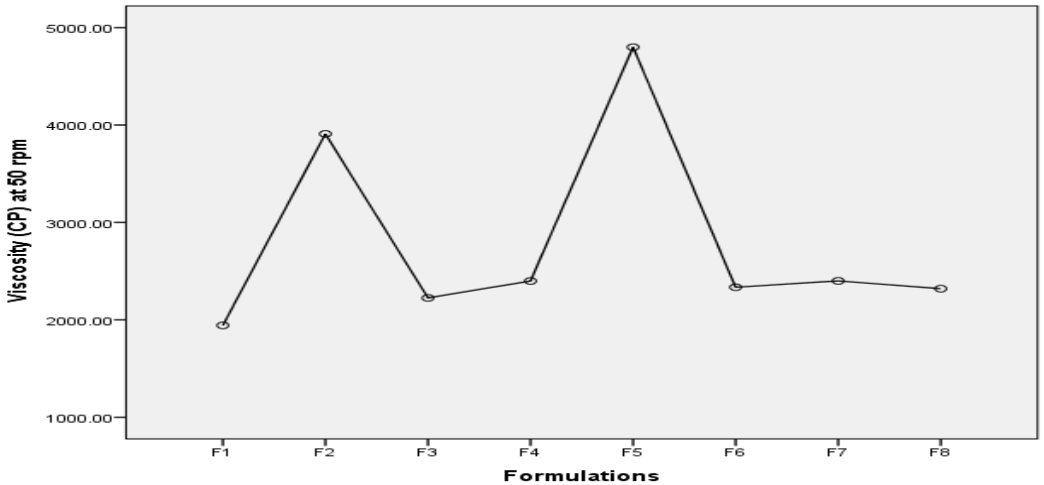


(a)

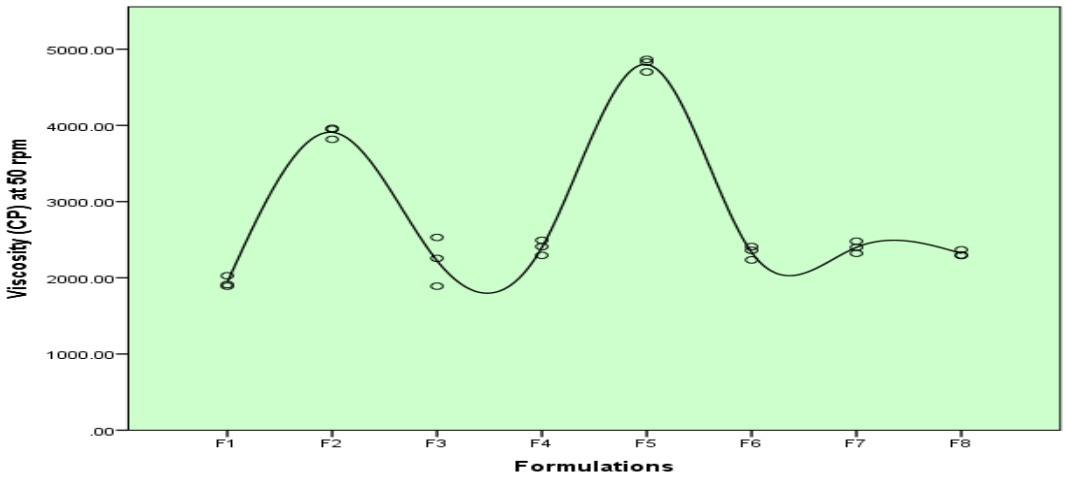


(b)

Figure 1: (a) and (b) Scatter dote shows moderate negative correlation between speradability values of oral gel bases and polymers concentrations (correlation= -0.3; *P*=0.02).

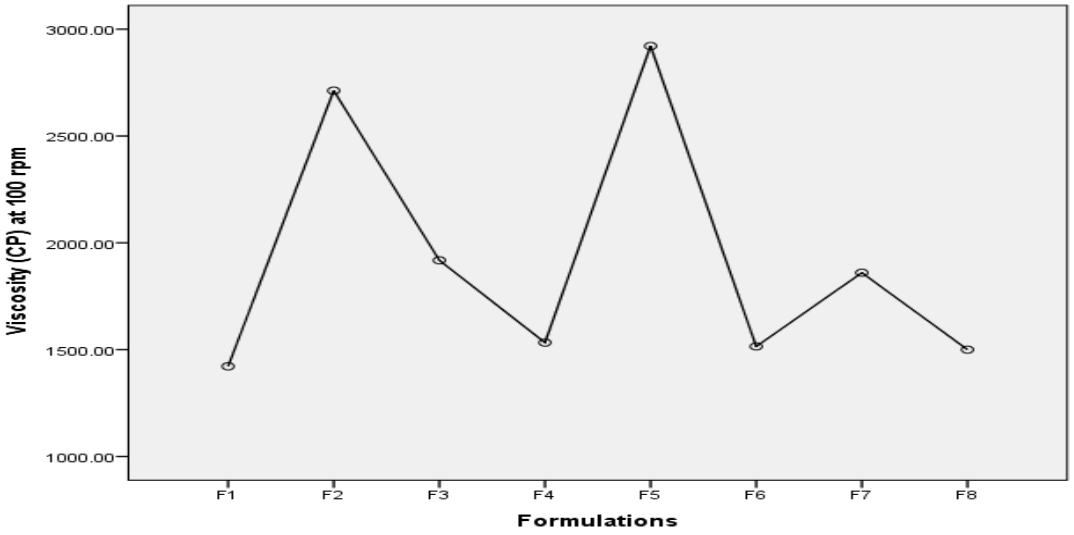


(i)

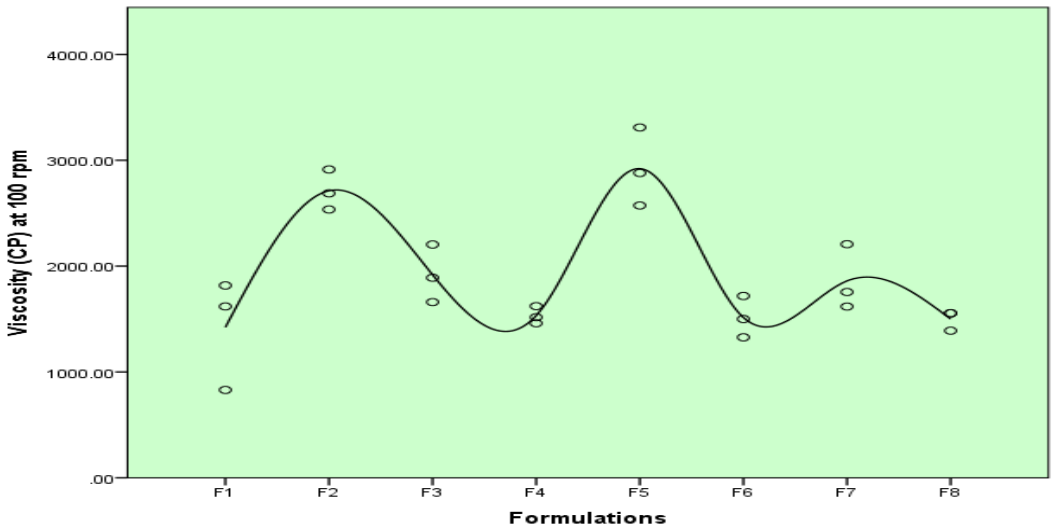


(ii)

Figure 2: i and ii: Scatter dote shows positive correlation between viscosity values at 50 rpm of oral gels and polymers concentrations (correlation= 0.1; *P*=0.05).



(iii)



(iv)

Figure 3: iii and iv: Scatter dote shows positive correlation between viscosity values at 100 rpm of oral gels and polymers concentrations (correlation= 0.2; *P*=0.04).

DISCUSSION

Experimental Design and Development of Formulations

One of the main ingredients of the gel formulation is the gelling agent. The concentration of viscosity enhancer or gel former is of immense value as a less concentration will lead to simple solution or lotion with very low consistency, while high concentration may lead to formation of gels with high viscosity leading to non-uniform distribution of drug and problem with handling of gel formulation. Two different gel formers (Natural and Synthetic) with various concentrations were tried in order to select the best. These concentrations of the gelling agents were selected in order to get oral gel base formulations were compatible and stable with acceptable physicochemical properties.

Carbopol polymer must be neutralized in order to achieve maximum viscosity. Once a neutralizer is added to the dispersion, thickening gradually occurs. Maximum viscosity is typically achieved at a pH of 6.0 - 7.0. The viscosity of Carbopol will begin to decrease at a pH of 9.0 and higher. This is caused by the presence of excess electrolytes which affect the electrostatic repulsion of the ionized carboxylic groups. In order to obtain high viscosity at pH values below 5 and above 9, an increased concentration of Carbopol is recommended. Additionally, use of a low concentration of polymer at low pH values should be avoided in an effort to achieve a robust formulation.

Eight different oral gel base formulations (F1 to F8) were prepared. It was compounded as indicated in (Table 1). Using 1% and 1.5% concentration of Carbopol 940 for F1 and F2 respectively. Formulations F3 to F8 were using different concentrations of Carbopol 940 combined with Xanthan gum as secondary gelling polymer, carbopol 940 were used as gelling agent in the formulation as they are biodegradable, bio-adhesive, biocompatible, irritation free and not absorbed into body. The percentage of polymers was selected after preparing the gel with various concentrations from 0.5 to 2.5%, where the 0.5 to 2% of carbopol 940 containing gels, above 2% concentration, the viscosity of the matrix is high, without interest for medical applications, and Xanthan gum 0.2% and 0.6% w/w was found to be compatible with the requirements of gel formulations. Triethanolamine was used in the formulations in order to adjust the pH of the formulation (6-7), The gelling effect of Carbopol is activated in two stages, firstly the dispersion and hydration of the Carbopol, and secondly "neutralizing" the solution by the addition of chemicals which increase the pH. Neutralizing agents include triethanolamine (TEA), sodium hydroxide and potassium hydroxide. In concord with some other researchers, increase of pH at constant polymer concentration gave us a decrease of flow index. In other words, increasing the pH gives the gel an increase in pseudoplastic character.[40] The manufacturer Noveon (Lubrizol Corporation) showed in one of their reports about Carbopol polymer, the relation between viscosity and pH. In their graphs the cohesiveness increased up to pH 6, remained stable from pH 6 to 10 and decreased from pH 10 and upwards. The manufacturer used in gel formulations the 18% NaOH as neutralizer while our neutralizer was triethylamine (TEA). TEA is a better neutralization agent than NaOH and Tromethamins (TRIS). There are a greater charge barrier in TEA layer than NaOH and TRIS. Binding ability of TEA cations to PAA is better than TRIS and NaOH and it gives a higher degree of polymer chain expansion.[41]

Glycerol is used as plasticizer (dispersant), sweetening agent and for it is emollient properties[42], it is also was used as plasticizer to increase the plasticity, and also to decrease the attraction between polymer chains to make them more flexible. make it possible to achieve improved compound processing characteristics, while also providing flexibility in the end-use product. methyl and propyl paraben as preservative and double distilled water.

Optimization of Developed Oral Gel Base Formulations

Optimization is the process of finding the best way of using the existing resources while taking into account all the factors that influence decisions in any experiment. It allows finding of the best possible value dependent variable by changing certain independent variables. The objectives of optimization involved to maintain the quality, reduce manufacturing costs, and safety of public and industry. Whereas the significance of optimizing a pharmaceutical product involved the discovery of important variables involved, cheaper and efficient way of formulating the product and improving the consistency and usefulness of quality specification in the formulation.[43]

One of the serious problems associated with the formulation and manufacture of topical–mucosal preparations is the establishment of reliable techniques for their characterization, mainly because of the complexity of their physical structure. Consumer preference for such products depends on various properties of the preparation, collectively known as the textural profile, which includes appearance, odor, extrudability (when applicable), initial sensations upon contact with the application site/s, spreading properties and tackiness after application.[44] Ultimate acceptability and clinical efficacy of such preparations require them to possess optimal mechanical properties (ease of removal from the container, spreadability on the substrate), rheological properties (viscosity, elasticity, thixotropy, flowability), and other desired properties such as desired drug release, and absorption.[45]

Poorly manufactured semi-solids may produce undesirable results that affect patient outcomes. Producing quality pharmaceutical gel literally boils down to physical appearance and physicochemical

characteristics. Therefore formulation factors affecting the physical appearance and physicochemical properties and performance of prepared oral gel bases were studied, particularly the effects of different polymer types, as well as itis different concentrations.

i. Effects of Polymer Type, Concentration and Polymer Combination at Different Concentrations on Sensory Properties and Physical Appearance

When locally applied formulation is being developed, sensory perceptions on texture, consistency and homogeneity are factors that need to be considered. These factors may directly determine overall patient experience and acceptance and can be extremely challenging. The sensory properties can be assessed by organoleptic analysis, But we surely have to bear in mind that the results from sensory evaluation are different from medicated and not medicated gel bases. Certainly, when gelling systems were medicated, differences in color are possible with subjective visual assessment. Same fact refers to odor and consistency assessment. From the presented results given in (Table 2), The gel bases were assessed for its sensory characteristics and qualities, The oral gel formulations had a smooth texture, clear, good consistency, free from particles and from viscous gel preparations with a smooth homogeneous appearance, it was concluded that all the formulated gel bases showed overall good physical appearance. The physical appearance of the oral gel bases was transparent for F1 and F2, whereas formulations F3-F8 white translucent, which were the color they got from the nature of the polymer/polymers used. Regardless the polymer/polymers presence and concentrations, there was no changes in other physical characteristics were observed between gel bases. All tested formulations had a good physical appearance.

The present study showed no significant difference in consistency and homogeneity when comparing different type and different polymer concentrations. Most likely, as already known, the polymer nature and it is concentration greatly impact the gel texture. Our results showed that all gel bases composed of these two polymers had homogenous texture and free of particles during the period of study. Overall pharmaceutical acceptability were satisfactory for all formulated gel bases. F1 and F2 had an advantage of providing an transparent appearance without having a negative impact on homogeneity and consistency.

ii. Effects of Polymer Type, Concentration and Polymer Combination at Different Concentrations on pH of The Gelling Systems

The salivary pH ranges from 5.5 to 7[46,47], The pH values of the oral gel bases were found to be in the range from 5.94 to 6.80, which was expected since the carbopol 940 was formulated with pH between 6 and 7 because these are values sufficient to obtain a good viscosity and clarity of the gel.[48]

It was found that pH values of all formulations, where in this range 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. This also indicated that the selected ingredients and polymers concentration of these formulations did not alter the pH of the formulations. The pH of various formulations is tabulated in (Table 3), 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.

iii. Effects of Polymer Type, Concentration and Polymer Combination at Different Concentrations on Spreadability and Extrudability

The efficacy of local therapy depends on the patient spreading the formulation in an even layer to deliver a standard dose. The optimum consistency of such a formulation helps ensure that a suitable dose is applied or delivered to the target site. 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 term spreadability denotes the extent of area to which a semisolid spreads on application to target sites. This feature determines such properties as ease of application on the surface, correct dosage transfer to the target site, ease of removal from the package, as well as consumer preference.[49,50] A product with poor spreadability fails to provide proper distribution of active pharmaceutical ingredients (APIs) and produces a negative patient reaction and has a high degree of application difficulty. The main factors effecting spreadability are temperature, consistency of the formulation, the rate and time of shear produced. The rate of spreading also depends on the viscosity of the formulation, the rate of evaporation of the solvent, and the rate of increase in viscosity with concentration that results from evaporation. Furthermore, strong cohesive forces within a formulation decrease its flowability, thus having a negative effect on spreading.

Spreadability is a very important property in the development of semisolid preparations meant for topical–mucosal routes. Because it is responsible for the overall performance of a formulation, it must be carefully taken into consideration and procedures must be devised for its effective measurement during the formulation development stages.

In this study the spreadability of the prepared oral gels was significantly (P = 0.001) decreased as the polymer concentration increased (F4, F5, and F6) compared with (F1, F2, and F3) respectively (Table 3 and Figure 1), 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.[51]

It observed that formulations with low carbopol 940 concentrations, showed the highest spreadability values (Table 3). increasing carbopol 940 concentration significantly ($P = 0.001$) reduce spreadability of prepared oral gel bases. It also observed that moderate negative correlation (Figure 1) between speradability values of oral gels and polymers concentrations (correlation = -0.3; $P = 0.02$).

Spreadability is an important property of oromucosal preparations from patient compliance point of view. A good gel takes less time to spread and will have high spreadability.[52] In general, the spreadability of gel decreased as the concentration of polymer increased.[53] Form the results, all the oral gel bases were found to have acceptable spreadability. It was observed that the spreadability tend to reduce upon increase in the concentration of polymers. This decrease in the spreadability with increase in the concentration of polymers can be attributed to the increase in the viscosity of the system.

Extrudability measures how easily a formulation can be squeeze from the container. Tube extrudability indicates the flow behavior of the product and may be used as a tool to predict a viscosity of the product. Although this approach is not perfectly accurate and perhaps too simplistic, the gel´s extrudability can reflect the gel´s viscosity. In fact, it is very common results for extrudability to estimate viscosity. Of course, better measuring techniques are available to quantify viscosity, but we decided to simplify the measurements assuming that extrudability, in principle, correlates with gel flow properties and viscosity in general.

The extrudability of gel was the parameter to measure energy that was used to extrude the gel out of the tube. If the gel was very viscous, the gel would be difficult to extrude out of the tube. Parameters measured were the volume of gel that came out of the tube due to application of 500gm load for 10 seconds given to the tube. All of gelling agent provided the significant contribution to extrudability properties of developed oral gel bases (Table 3). It was observed that the extrudability tend to reduce upon increase in the concentration of polymers. The trend was similar in all the polymers studied. Since the packing of gels have gained a considerable importance in delivery of desired quantity of gel from jar or extrusion of gel from collapsible tube, therefore measurement of extrudability becomes an important criterion for gels.[54]

iv. Effects of Polymer Type, Concentration and Polymer Combination at Different Concentrations on Viscosity of The Prepared Oral Gels

The measurement of viscosity provides a better understanding of consistency, homogeneity and overall quality of gels. Viscosities influence the drug delivery and also drug diffusion rate.

The viscosity of gels were determined by using HAAKE Viscometer 6plus at two different rpm, Viscosities of all formulations at 50 and 100 rpm are shown in (Table 4, Figure 2 and 3) shows viscosity profile of all formulations. The viscosity of the gel bases was evaluated and it was found the viscosity of these gels decreases with increasing rate of shear, showed with non-Newtonian flow (shear thinning). Shear thinning phenomenon, an advantageous property of buccal gel, was observed for all the gel tested.

The viscosity of the prepared oral gel bases was significantly ($p<0.05$) affected by polymer type and it was found in the following order: carbopol 940> carbopol/ xanthan gum combination found in (F1and F2) and (F3 – F8) respectively as shown in table 4 and figures 2-3. It was observed that increasing polymer concentration led to a significant ($p<0.05$) increase in gel viscosity.

For formulations containing carbopol alone, F2 containing carbopol 940 at concentration 1.5% possessed the highest viscosity value. As general the concentration of polymer was increased, the viscosity of formulation was also increased.

The study shows positive correlation (Figure 2 i and ii) between viscosity values at 50 rpm of oral gel bases and polymers concentrations (correlation = 0.1; $P = 0.05$), and also shows positive correlation (Figure 3 iii and iv) between viscosity values at 100 rpm of oral gels and polymers concentrations (correlation = 0.2; $P = 0.04$).

With respect to the combined polymer, it was found that the F5 containing (carbopol 940 1.5% and xanthan gum 0.2%) possessed the highest viscosity value. Although, the remarkable high viscosity of xanthan gum may be attributed to its anionic nature. The electrostatic repulsions from the charged groups on the side chains make its molecules extend.[55] Because of this, the molecules align and associate via hydrogen bonding to form a weakly structured helical conformation which would immobilize the free water and increase the viscosity. In addition, the higher viscosity of xanthan gum is probably also related to its high molecular weight (approximately two million Daltons)[56] which increases the intermolecular association among polymer chains. in spite of the increase in the xanthan gum concentrations in the formulated gel bases F7 and F8 of 0.6%w/w, and by comparing their results of viscosity values of formulations F3 and F4 which containing the same carbopol 940 concentrations of 0.5% and 1%w/w respectively and xanthan gum at concentration of 0.2%w/w, these results may be explained by the low percent modification in viscosity as increasing xanthan gum concentration.

The behaviour of formulations varied with the polymer concentration, the use of Xanthan gum as secondary thickening agent effect was observed to have no

descriptive variation on the viscosity of the formulations. Carbopol 940 use at 0.5% to 2% in the gel formulations showed descriptive results on the viscosity and physicochemical properties, it was seen to be more contribute to the viscosity behavior of formulations.

The study also showed that, by comparing viscosity values of formulations containing combined polymers (F3–F8) with that containing only carbopol 1.5% (F2), only increase in viscosity was detected in F5. This leads to the conclusion that, viscosity of different formulations was mainly due to the presence of carbopol 940, higher viscosity value of F2 indicating higher consistency which may be due to its cross –linked structure and the molecular weight between cross link, reflects this rheological behavior.[57]

Viscosity of a gel formulation directly affects the release of active ingredients from the formulation. Generally, the viscosity of gel formulations reflects consistency. High viscosity of a gel formulation negatively affects the release of active substances from the formulations and consequently reduce it is therapeutic effectiveness, also if the viscosity is too high, this will result in irritation & difficulty in application and if it is too low, it will give rise to an increased drainage. So, the formulation should have an optimum viscosity for easy and good efficiency on mucosal application.

Selection of Optimum Formulas

All the prepared formulas are subjected to characteristic's analysis in order to select the optimum formula/s, developed oral gel bases (F1 and F4) were selected as an optimum formulas since it have good spreading behaviour and excellent extrudability, in addition to pH value of 6.80 and 6.33 for F1 and F4 respectively, which is within the range of healthy oral cavity. Thus, it may be assumed that these formulations are applicable for oral mucosa and can be used without the risk of irritancy. Additionally F1 and F4 have an acceptable physical and sensory properties, homogeneity, consistency and viscosity, but F1 had an advantage of providing an transparent appearance without having a negative impact on homogeneity and consistency.

CONCLUSION

Local delivery of drugs for the treatment of mucosal diseases is able to reduce side effects and improve treatment outcomes. It can be concluded from the present investigation that proper selection of polymers is a prerequisite for designing and developing a local oromucosal drug delivery system.

The presented work envisages the feasibility of the use of the carbopol 940 as gelling agent and in combination with xanthan gum at different concentrations as good oral gel bases for local oral drug delivery system for local oromucosal infectious diseases.

Oral gels should have acceptable physical and chemical parameters and should also be stable over the period of use These parameters include the viscosity, pH, spreadability, extrudability etc, under the suitable storage conditions.

As expected, the natural and synthetic polymer form a better formulations. This study suggests variable concentrations of gelling agents as vehicles for oromucosal gels. Hence, it gives the formulator more options other than the limited available gels used frequently as oral gels.

In this contribution, we developed and evaluated the oral gel bases with the different concentrations of carbopol 940 and xanthan gum to obtain the optimized Formulations which is suited for application as an local oral gel delivery system of drugs for treatment of local oromucosal diseases.

The potential for topical delivery systems in oral medicine has not yet been fully realized and further research targeted to oral medicine applications is needed in order to improve treatment outcomes.

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