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Original Article

TREATMENT OF MOUTH ULCER BY CURCUMIN LOADED THERMOREVERSIBLE MUCOADHESIVE GEL: A TECHNICAL NOTE

YOGESH S. THORAT*[1], ASHA M. SARVAGOD[1], SHITAL V. KULKARNI[1], AVINASH H. HOSMANI[2]

[1]D. S. T. S. Mandal's College of Pharmacy, Solapur, Maharashtra, [2]Govt. College of Pharmacy, Ranagiri, Maharashtra
Email: ysthorat@rediffmail.com

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ABSTRACT

Objective: Mouth ulcer is one of the commonest disorders caused due to a variety of etiological factors. Although many formulations like solution, suspension and ointments are commercially available, no therapy can be said completely useful for the treatment of mouth ulcers. The efficacy of the therapy can be improved by the approach of bio adhesion. The phenomenon of sol to gel conversion can be useful due to its ease of administration compared to gel formulations. Curcumin is known to have wound healing, anti-carcinogenic and anti-bacterial activities can be effective in treatment of mouth ulcers.

Methods: Hence, the present study was aimed to formulate Thermo reversible Mucoadhesive Gel (TMG) containing Curcumin for treatment of mouth ulcer. Formulations were prepared by using Pluronic F68 and Pluronic F127 as thermo reversible agent along with carbomers and Xanthan gum as bioadhesive polymers. The formulations were characterized for gelation temperature, pH, gel strength, spreadability, *in vitro* muco adhesion and *in vitro* drug release.

Results: Increase in the concentration of mucoadhesive agent enhanced the mucoadhesive force significantly. All batches were found to be satisfactory results for gelation temperature, Gel strength, Muco adhesion studies, Spreadability, gelling capacity, *In-vitro* drug release etc. The formulations delivered drug for about 4 h.

Conclusion: The obtained results show that the residence time as well as the contact area of curcumin at the ulcer can be enhanced along with a sustained release. It can be concluded that TMG of Curcumin can be ideal candidate for mouth ulcer.

Keywords: Carbomer, Curcumin, Thermoreversible Mouth ulcer, Mucoadhesive gel, Poloxamers.

INTRODUCTION

Mouth ulcers [1, 2] are painful round or oval sores that form in the mouth, most often on the inside of the cheeks or lips. Common causes of mouth ulcers include nutritional deficiencies such as iron, vitamins, especially B_{12} and C, poor oral hygiene, infections, stress, indigestion, mechanical injury, food allergies, hormonal imbalance, skin disease etc. Mouth ulcers, also known as apthous ulcers, can be painful when eating, drinking or brushing teeth.

Curcumin [3, 4] is an orange-yellow crystalline powder obtained from rhizome of *Curcuma longa*, family *zingiberaceae*. Turmeric and curcumin are believed to have anti-inflammatory, antioxidant, and even anticancer properties. Curcumin protects against types of skin diseases, Alzheimer's disease, colitis and gastric ulcers. Curcumin also shows wound healing activities effective in treatment of mouth ulcers by increasing cellular proliferation and collagen synthesis at the wound site as evidenced by increasing in DNA, total protein and type-III collagen content of wound tissue leading to faster rate of epithelilisation, wound contraction and increases tensile strength.

Muco adhesive drug delivery system [5] remains in close contact with the absorption tissue, the mucous membrane, releasing the drug at the action site leading to better bioavailability and both local and systemic effects. The potential use for mucoadhesive systems as drug carriers lies in its prolongation of the residence time at the absorption site, allowing intensified contact with the epithelial barrier. Application of stimuli sensitive drug delivery approach like *in situ* thermo-reversible polymers along with mucoadhesive system, improves the effectiveness and patient compliance of the dosage form [6].

The principles of the bioadhesion and stimuli sensitive drug delivery systems can be combined together. Bio adhesion can increase the residence time and the contact area of drug at the site of action. This will be advantageous over the conventionally used gels and semisolid preparations which are readily washed-off by the salivation process. The thermo reversible nature of the gel will impart an ease of administration.

Hence, the objective of the present study was to formulate thermoreversible mucoadhesive gel containing curcumin for the better therapy of mouth ulcer by improving the contact time around the mucosal lesion imparting the wound healing activity.

MATERIALS AND METHODS

Materials

Curcuma longa rhizomes were obtained from the local supplier and authenticated. Pluronic F127 and Pluronic F 68 were kindly supplied as a gift sample from BASF Ltd, Mumbai. Carbopol 971P and Carbopol 974P were obtained as gift sample from Noveon Ltd, Mumbai. Xanthan gum was obtained as gift sample from Ozone International, Mumbai. Other chemicals were of laboratory grade.

Extraction of curcumin

Curcumin was extracted from rhizomes of *Curcuma longa* using soxhlet apparatus [7]. Approximately 100 g of coarse particles of turmeric was loaded in the a paper thimble in a glass container and extraction was carried out using 500 ml of 70% methanol under continuous heating and reflux. The procedure was monitored until the yellow colour of the extractions faded after 72 h. The extract yielded about 4 g of curcumin.

Authentication of curcumin

The authentication of the obtained curcumin was done using Thin Layer Chromatography (TLC) and UV-Spectrophotometry [8]. TLC was performed using Silica gel G as stationary phase and Chloroform: Ethanol: Glacial acetic acid (94:5:1) as mobile phase. R_f value of the sample was found to be 0.78. The λmax of the sample was observed to be 280 nm. These values comply with the standard.

Preparation of mucoadhesive thermo reversible gel

Plain and medicated thermo reversible mucoadhesive in situ gels were prepared using the cold method [9]. Plain *in situ* gels were formulated using different concentrations of Pluronic F68 and

Pluronic F127 [6] to give gelation at the temperature range in oral cavity i.e. 33-37 °C. Poloxamers were added to cold distilled water with continuous agitation and kept overnight at 5-7 °C until clear solutions were obtained. Curcumin (1% w/w) and mucoadhesive polymers (table 1) were added to the Poloxamer solutions with constant stirring [10].

Table 1: Formulation of thermo reversible mucoadhesive gel

Formulation code	Curcumin (%w/v)	Pluronic F 127 (%)	Pluronic F 68 (%)	Carbopol 971 P (%)	Carbopol 974 P (%)	Xanthan gum (%)
F1	1	25	5	0.2	-	-
F2	1	25	5	0.4	-	-
F3	1	25	5	0.6	-	-
F4	1	25	5	0.8	-	-
F5	1	25	5	1	-	-
F6	1	25	5	-	0.2	-
F7	1	25	5	-	0.4	-
F8	1	25	5	-	0.6	-
F9	1	25	5	-	0.8	-
F10	1	25	5	-	1	-
F11	1	25	5	-	-	0.2
F12	1	25	5	-	-	0.4
F13	1	25	5	-	-	0.6
F14	1	25	5	-	-	0.8
F15	1	25	5	-	-	1

Evaluation of thermo reversible mucoadhesive gel

Gelation temperature

A 2 ml aliquot of the prepared solution was transferred to a test tube and put in a water bath. The temperature of the bath was slowly increased in the increment of 1 °C per minute till the occurrence of sol-gel transition. Sol-gel transition was confirmed when the meniscus would no longer move upon tilting through 90 °[9, 11]. The readings were taken in triplicates.

pH

pH is an important parameter in order to avoid the irritability of the formulation to the mucus membrane. About 5 g of the solution was weighed accurately and diluted with 45 ml of water. pH of the solution was determine the at 27 °C using the pH meter (pH Systronics digital pH meter).

Spreadability

For the determination of spreadability, a lab-fabricated apparatus was used. The apparatus consists of a glass slides fixed on a wooden block with a pulley. Another glass slide is kept over the fixed slide and is attached with a string running over the pulley. A fixed weight is attached to the free end of the string. Sample of TMG was applied in between two glass slides and was compressed to uniform thickness by placing 2 g weight for 1 min. The time (t) in which the upper glass slide moves over to the lower slide upto the predefined length (L) was measured. The spreadability (S) was calculated by the formula:

$$S = ML/t.$$

Gelling capacity

The gelling capacity of the formed gel was determined using visual inspection and the different grades were allotted as per the gel integrity, consistency, reproducibility and rate of gelation.

Measurement of gel strength

Measurement of gel strength was done by the previously reported method [9]. A sample of 1 g of gel was placed in the apparatus and gelled in a thermostat at 37 °C. Weight was applied to gel and minimum weight required to penetrate up to 5 cm in the gel matrix was measured.

Muco adhesive studies

Mucoadhesive strength was determined in term of detachment stress i.e. force required to detach the formulation from the mucosal surface. Mucoadhesive strengths of gel was determined by using the modified method [12] Intestinal mucosa was obtained from the local slaughterhouse and mounted on surface using adhesive tape while another mucosal section was fixed in inverted position to the cylinder. 50 mg of gel was placed on the mucosal surface. The glass mounted mucosal surface with gel formulation and mucosal surface attached to cylinder were held in contact with each other for 2 min to ensure intimate contact between them. In second pan, the weights were added until two layers of mucosa get detached from each other. The nasal mucosa was changed for each measurement.

Drug release studies

Release of the curcumin from TMG was studied by using the Franz Diffusion cell apparatus. A cellophane membrane was pre-soaked in phosphate buffer pH 6.8. 1 g of medicament was kept in permeation cell. Receptor compartment was containing 15 ml of 6.8 pH phosphate buffer solutions agitated using a magnetic stirrer at the temperature 37 °C±1 °C. 2 ml aliquots were withdrawn periodically maintaining sink condition. Curcumin content was assayed at 280 nm after suitable dilutions [13].

RESULTS AND DISCUSSION

Gelation temperature

The temperature of oral cavity is 33-37°C. At higher temperature Poly-oxy-ethylene (POE) and Poly-oxy-propylene (POP) fragments of Poloxamer get cross-linked to yield a gel like structure. The proportion of Pluronic F68 and Pluronic F127 in the formulation batches was optimized to show the gelation temperature at about 33-34°C. It was observed of Curcumin lowers the temperature while addition of mucoadhesive polymer increases the gelation temperature. Hence the prepared formulations ensure the sol to gel transformation in oral cavity. The sol form will be easy to administer compared to ointments and gels while the gel form will adhere to mucosal lining.

Gel strength

Gel strength is indicative of the tensile strength of the gelled mass. It signifies the ability of the gelled mass to withstand *in-vivo*. Table 2 reveal the gel strength of the formulation containing various concentrations of Carbopol 971P, Carbopol 974P and xanthan gum was found to be gradually increased. Formulation containing Carbopol 971 P shows higher gel strength. This can be attributed to the cross-linking behavior of Carbopols. [10]

Muco adhesive strength

Formulation contained mucoadhesive polymers in various increasing concentrations. As reported in the previous literatures, mucoadhesive strength of gels was found to be increased with increasing concentration of mucoadhesive polymers as shown in table 2.

Formulations containing Carbopol 971P in lowest concentration as 0.2% shows higher mucoadhesive property as compared to Carbopol 974P and Xanthan gum. The reason behind higher mucoadhesive strength of carbomers than that of the natural polymers is higher molecular content of hydrophilic groups in the structure which impart higher hydrophilicity leading to greater swelling as well as higher interaction with the hydrophilic groups on mucin. The interaction between mucin and polymer is responsible for the better mucoadhesive force as per the wetting theory of muco adhesion [10].

Gelling capacity

The prepared formulations were shown good gelling capacity. The concentration of mucoadhesive polymers increases, the gelling capacity was found to be better. Gelling in the *in situ* gelation system containing Poloxamers is due to the cross-linking of POP and POE units of the Poloxamers [6]. The fact that Carbopols get cross-linked can be thought to assist the Poloxamer gels to gain a better consistency.

Spreadability

All formulations in the sol phase were found to be good spreadability. Formulations containing Carbopol 971P were found to be spreadability ranges from 3-4.1. Formulations containing Carbopol 974P were found to be spreadability ranges from 3.0-3.7 and Formulations containing Xanthan gum were found to be spreadability ranges from 3-3.8.

Table 2: Measurement of Gelation temperature

Batch code	Gelation temperature (°C)*	Gel strength (g)*	Mucoadhesive strength (dynes/cm)2*	Gelling capacity	Spreadability (sec)*
F1	34±0.33	17.62±1.00	8354±506.8	+	3.6±0.02
F2	33±0.67	22.87±1.52	9432.5±100.3	+	3.41±0.52
F3	34±0.15	27.78±3.50	11335±253.4	++	3.7±0.03
F4	34±0.33	32.25±3.00	12254.3±214.4	+++	4.10±0.03
F5	33±0.05	44.97±1.67	14722.8±623.3	+++	3.76±0.32
F6	33±0.67	17.20±1.33	6615±55.3	+	3±0.00
F7	34±0.54	18.98±0.67	8607.6±732.1	++	3.13±0.33
F8	33±0.67	20.25±0.33	10512.1±451.1	++	3.69±0.23
F9	33±0.33	27.10±4.15	12730.2±502.4	+++	3.77±0.12
F10	34±0.51	32.05±2.33	13403.1±58.2	+++	3.5±0.00
F11	32±0.33	19.20±1.67	6863.2±340.4	+	3.19±0.33
F12	34±0.00	25.11±0.67	8950.6±512.2	++	3.16±0.67
F13	33±0.67	29.24±1.23	11861.2±1053.2	++	3.77±1.00
F14	34±1.00	31.01±2.00	12887±232.6	+++	3.85±0.03
F15	33±0.33	33.10±1.33	14737.6±88.2	+++	3.07±0.15

* n=3, mean±SD

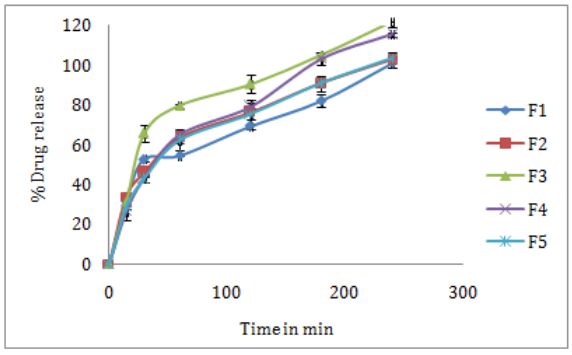

Fig. 1: *In-vitro* drug release profile of F1 to F5
*** n=3, mean±SD *In vitro* drug release study**

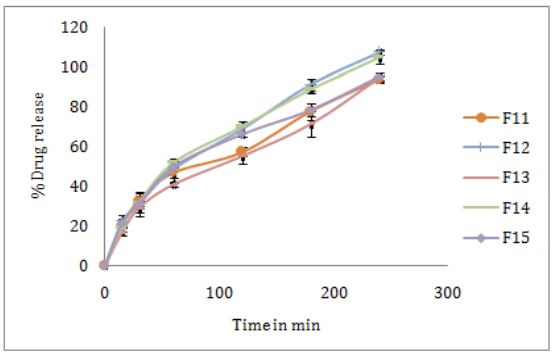

Fig. 3: In-vitro drug release profile of F11 to F15
*** n=3, mean±SD**

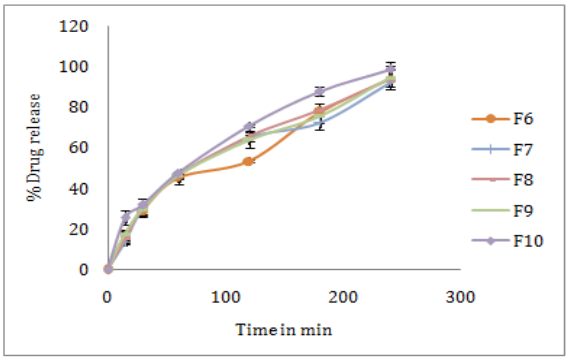

Fig. 2: *In-vitro* drug release profile of F6 to F10
*** n=3, mean±SD**

The *In-vitro* drug release profile of Curcumin from TMGs was studied. It was found that the release of curcumin was extended to 4 h by most of the preparation. This ensures that the mouth ulcer can be efficiently treated. From dissolution studies it was revealed that increasing concentrations of mucoadhesive polymers were responsible for the drug release retardation effect (fig. 1 to 3). A correlation can be observed between the results of gel strength and *in vitro* dissolution. The drug dissolution mechanism from the gel structure is matrix diffusion. Hence greater gelation results in the slower and retarded rate of diffusion due to the effect of more cross-links resulting in the fewer paths for the water drags and slower penetration.

CONCLUSION

The attempt was done to bridge the indigenous knowledge of medicine with the modern and novel drug delivery system by formulating mucoadhesive thermo reversible sol gel system of

Curcumin using thermo reversible polymers such as Pluronic F127/Pluronic F68 and mucoadhesive polymers such as Carbopol 971P, Carbopol 974P or Xanthan gum. The prepared formulations were shown the gelation temperature at about 33-34°C. All batches were found to be satisfactory results for gelation temperature, Gel strength, Mucoadhesion studies, Spreadability, gelling capacity, *In-vitro* drug release etc. The formulated drug delivery system was found to be delivering the drug over an extended period of time for about 4 h. Hence, it can be concluded that the mucoadhesive gel of Curcumin is an ideal candidate for mouth ulcer.

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CONFLICT OF INTERESTS

Declared None

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