Formulation of Choline Salicylate as Lozenge Tablet for Improved Delivery to Oral Cavity

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Accepted 12 March 2000
Revised 24 February 2000
Received 25 September 1999

Choline salicylate was formulated as a lozenge tablet to provide prolonged relief from pain associated with mouth ulcers. The lozenges were prepared using mannitol as base and gelatin dispersion as binder. The composition of optimized tablet was; choline salicylate, 20 mg; HPMC-E15, 20 mg; CP 934P, 4 mg; gelatin, 50 mg; mannitol, 896.5 mg; magnesium stearate, 5 mg; cetrimide, 0.5 mg; aspartame, 0.4 mg and flavour. Dissolution studies showed 95% release of drug in 65 min. In mouth, salivary concentration was 130.00 $\mu g/ml^{-1}$. The hardness of tablet was 10.44 $kg.cm^{-2}$ and they were non-gritty and had good mouthfeel, taste and comfort. Lozenge tablet formulation can provide an attractive alternative formulation in the alleviation of pain in recurrent aphthous mucosal ulcers.

Oral mucosal ulceration is a frequently encountered oral disorder and the common form of this disease is recurrent aphthous ulceration (RAU) or canker sores[1-5]. commercially choline salicylate gel is available for relief of pain but that provides only short term relief. The present work is aimed at preparing a formulation of choline salicylate as lozenge tablet which would provide sustained effect in relief of pain associated with discrete ulceration[6,7]. To achieve the goal of providing prolonged effect, lozenges were prepared along with polymers, which would produce effective levels of drug for a period of approximately 1h. Choline salicylate was obtained as a gift sample from Sam International, Mumbai. Gelatin, Sodium CMC, CMC, tragacanth, guar gum, HPMC E15, Carbopol® 934P and HPC-M were obtained from Dabur Research Foundation, Sahibabad. Other reagents and chemicals used were of analytical grade.

The ingredients (choline salicylate, HPMC E15, Carbopol 934P, mannitol aspartame, citrimide and flavor) were mixed by trituration and the formulation was prepared by wet granulation process, using gelatin solution as binder. The wet mass prepared was passed through #8 sieve and the granules obtained were dried under vacuum at 25±1° for 40 min. Dried granules were subjected to screening and #22/40 fraction was collected for further processing. After addition of suitable lubricants and fines the granules were compressed using a four punch tabletting machine (Dhiman Eng. Works). Each lozenge weighed approximately 1.0 g with a thickness of 4.0 ±0.1 mm and a diameter of 12.0 mm.

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The dissolution test apparatus (USP II) consisted of a 150 ml glass beaker with a diameter of 50 mm which was surrounded by a water jacket provided with a thermostat to maintain the temperature at 37±0.5°. The dissolution medium (phosphate buffer, pH 6.6 USPXXIII; 100 ml)[8] was placed in the beaker containing the lozenge and was mechanically stirred at 100 rpm. At various time intervals samples of dissolution fluid were withdrawn and replaced immediately with an equal volume of fresh fluid. The samples were analyzed colorimetrically (Spectronic 21, Bausch & Lomb) at 530 nm after developing complex with ferric chloride coloring reagent[9]. Graph was plotted between the cumulative percentage drug released in the fluid and time (Fig. 1).

The method used to determine surface pH of the formulation was similar to that used by Bottenberg *et al.*[10]. A combined glass electrode was used for the purpose. The lozenges were allowed to swell by keeping them in contact with 1.0 ml of distilled water (pH 6.6±0.05) for two hours and pH was noted by bringing the electrode in contact with the surface of the formulations. The hardness of prepared lozenges was determined using Monsanto hardness tester (Cadmach, (India). Test for

grittiness was done by partially dissolving the lozenges under running tap water, until one third to half of the tablets washed off[11]. These partially dissolved lozenges were rubbed between thumb and forefingers to check any grittiness.

A modified version of Franz diffusion cell[12] was used to see the permeation of the drug across the mucous membrane into the systemic circulation. Upper chamber, which was open from above, harbored the bovine mucosa at the base. Lower chamber contained a sampling port and a teflon coated magnetic needle. The skin was held in between the two chambers in such a manner that it did not shift from its place. Upper chamber contained 10.0 ml of phosphate buffer pH 6.6 whereas the lower chamber contained buffer of pH 7.4. The cell was allowed to stabilize for about 4.0 h and then the tablet was kept over the membrane. Samples (2 ml) were withdrawn from the lower chamber periodically and permeated drug was determined colorimetrically.

In vivo evaluation was done to determine the time of complete erosion of the optimized lozenges and the same was compared with *in vitro* erosion time. The volunteers (five in number) were instructed not to eat at least one hour prior to the study and eating and drinking were restricted during the study. The lozenges were allowed to dissolve slowly in the mouth. Salivary samples were taken at different time intervals over a period of one hour and were evaluated for drug content. The samples were centrifuged at 1500 rpm for 4 min, 1 ml of the supernatant was diluted with 5 ml of water and to it was added 4 ml of ferric chloride coloring reagent. The samples were analyzed at 530 nm. The results are given in Table 1. C_{max} and T_{max} were determined as shown in Table 2. AUC (to-tn) till the last sampling time was calculated. Coefficient of correlation between the mean time of complete erosion, *in vitro* and *in vivo* was determined.

Stability studies were performed according to WHO guidelines to determine the effect of the presence of formulation additives on the stability of the formulation under accelerated storage condition of temperature, high humidity and UV rays. Effect on surface pH, release studies, hardness and friability was tested.

Selection of polymers was based on the results of release studies, hardness and surface pH. Carbopol® 934P was found to delay the release of choline salicylate but at the same time increased the hardness of the lozenge tablets. Dissolution profile of the optimized tablet is

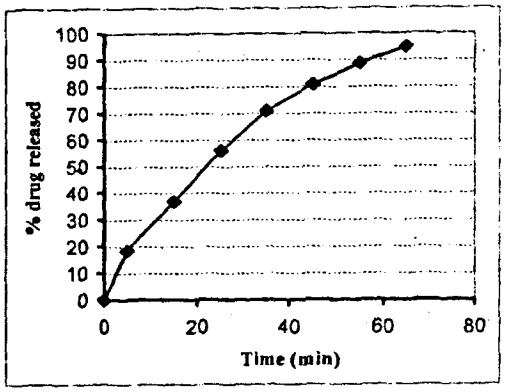

Fig. 1 : Dissolution profile of the optimized lozenge tablet

Dissolution test was performed using USP II apparatus with phosphate buffer, pH 6.6 as the dissolution medium, which was stirred continuously at 100 rpm.

given in Fig. 1. Lozenges passed the weight variation and content uniformity test. Average hardness was found to be 10.44 $kg.cm^{-2}$. No grittiness was felt for any of the lozenges. Among all the formulations developed the optimized formulation exhibited 94.88% drug release in 65 min, *in vitro*. Surface pH of the formulation was found to be in the range of 6.0-7.0 $T_{90\%}$ was found to be 41.0 min. Carbopol® 934 P was included in the formulations as earlier studies on treatment of recurrent aphthous ulceration have revealed that hydroxypropyl cellulose and HPMC after esterification with carboxyl groups gave a continuous bioadhesive film on the inner surface of oral mucosa which protested the ulcers from trauma and irritants for approximately 4 to 6 h[13].

In healthy human volunteers the mean salivary concentration ranged from 130-232 $\mu g.ml^{-1}$ and time of complete erosion ranged from 52.0 to 66.0 min. A correlation co-efficient of 0.95494 was obtained between mean time of complete erosion attained *in vivo* and *in vitro*, which was statistically significant at 5% confidence level. AUC was found to be 13720 $\mu g.min^{-1}.ml^{-1}$ whereas the C_{max} was 238.0 $\mu g.ml^{-1}$ and t_{max} was 27.0 min. Permeation studies showed that only 0.51% drug permeated through bovine mucosa over a period of 6.0 h, which ensures the availability of the drug locally in the oral cavity.

Stability studies (at 40°/75% RH for 3 m) indicated that the decrease in drug content was less than 5.0 per cent. There was negligible effect on surface pH, hardness, friability etc after completion of stability study. Even in UV chamber the loss in drug content was <5.0% over a period of 3.0 m. Thus the shelf life of the proposed

TABLE 1 : DRUG LEVELS IN SALIVA OF HUMAN VOLUNTEERS

Time (min)	Salivary concentration of Choline Salicylate ($\mu g.ml^{-1}$)					Mean salivary concentration ($\mu g.ml^{-1}$)
	I	II	III	IV	V	
5	200	210	210	170	190	196±16.73
15	220	200	230	190	210	210±15.81
25	250	230	210	230	240	232±14.80
35	230	200	240	200	210	216±18.16
45	190	170	180	190	170	180±10.00
55	170	160	170	160	140	160±12.24
65	140	130	140	130	110	130±12.24

Salivary concentration at each sampling point is expressed as mean±standard deviation of the concentration obtained from 5 volunteers

TABLE 2 : IMPORTANT PARAMETERS AS STUDIED IN HUMAN VOLUNTEERS

Parameter	Volunteer					Average
	I	II	III	IV	V	
Time of erosion (min)	60	68.3	55	65.3	52.3	60.18±6.72
C_{max} ($\mu g/ml$)	250	230	240	230	240	238±8.36
t_{max} (min)	25	25	35	25	25	27±4.47
AUC 0-65 min ($\mu g/min.ml-1$)	12800	11825	12575	15450	15950	13720± 1851

Each parameter is expressed as mean±standard deviation of the values obtained from 5 volunteers

formulation is at least 24 m. The optimized formulation did not cause any excessive salivation. No irritation or grittiness was reported by the volunteers. The proposed formulation provides an attractive alternative dosage form for choline salicylate for the relief of pain associated with mouth ulcers.

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