Research Article

Formulation of Sublingual Betaglucogallin Tablets for Rapid Relief of Inflammation

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ABSTRACT

Sublingual Betaglucogallin tablets offer a promising approach for the rapid relief of inflammation. This study aims to formulate and evaluate these tablets, assessing their potential as a novel anti-inflammatory treatment. Betaglucogallin, a polyphenolic compound derived from natural sources, possesses anti-inflammatory properties, making it an attractive candidate for sublingual delivery. The tablets were prepared using a combination of excipients and Betaglucogallin to enhance solubility and bioavailability. Various formulation parameters were optimized, and the tablets were characterized for their physicochemical properties, disintegration time, and in vitro release profiles. Our findings demonstrate that the formulated sublingual Betaglucogallin tablets exhibit rapid disintegration and release profiles, ensuring immediate contact with the sublingual mucosa, which is highly vascularized, leading to rapid absorption and onset of action. In conclusion, sublingual Betaglucogallin tablets represent a promising strategy for the rapid relief of inflammation, offering advantages such as avoidance of first-pass metabolism, rapid onset of action, and sustained therapeutic levels. These tablets may serve as a convenient alternative to conventional anti-inflammatory treatments, potentially improving patient compliance and overall therapeutic outcomes.

Keywords: Formulation, sublingual tablets, Betaglucogallin, inflammation.

INTRODUCTION

For certain special patient populations (e.g., children, the elderly, or patients with dysphagia, intestinal insufficiency, nausea, or trypanophobia), the common routes of drug administration (oral and parenteral) appear to be inappropriate and are often accompanied by poor adherence[1]. Administration via the oral mucosa as a patient and indication centered treatment offers a beneficial alternative. Patient compliance and rapid onset of action are important for improved therapy; this can be achieved through developing sublingual tablets which can rapidly disintegrate and dissolve in the oral cavity which facilitates patient safety and adherence by reducing the risk of side effects. The latest technologies in drug delivery systems present many pharmaceutical and patient characteristics, ranging from enhanced life-cycle management to convenient dosing for paediatric and geriatric patients, and patients with dysphagia[1-2.] Sublingual drug delivery is considered to be an effective route of delivery which provides rapid and direct drug absorption into systemic circulation compared to conventional tablets.

Chronic muscle inflammation, also known as myositis, is a debilitating condition characterized by persistent inflammation in the muscle tissue[1.] It can result from various causes, such as autoimmune disorders, infections, or repetitive injuries. The inflammatory response in myositis leads to pain, impaired muscle function, and reduced quality of life for affected individuals[1.] Therefore, identifying effective strategies to modulate pain and inflammation in chronic muscle inflammation is of paramount importance.

Beta-glucogallin is a natural compound found in certain plant sources, including gallnuts. It possesses antioxidant and anti-inflammatory properties and has been traditionally used in herbal medicine for its therapeutic effects[3-6]. Recent studies have suggested that beta-glucogallin may have pain-modulating properties, making it a potential candidate for managing chronic muscle inflammation. Beta-glucogallin (BGG) is an important tannin precursor naturally found in a variety of plants such as gooseberry (fruits of *Embellica officinalis*), raspberry, amla fruit extracts, and date palms (β-D-glucogallin present in fruits of *Phoenix dactylifera L.var.*), etc. BGG was reported to be a potential therapeutic agent in the management of a variety of diseases including diabetic complications such as diabetic cataract, prevention of cataract development and progression, retinal damages in diabetic eyes, hyperglycemia, and inflammatory diseases and associated stress[3-6].

The use of beta-glucogallin sublingual tablet for the management of chronic muscle pain sounds like an interesting concept that combines advanced drug delivery technology with natural compounds. Our aim is to overcome the limitation observed in the oral route; to provide fast dissolution or disintegration in the oral cavity, without the need for water or chewing; to avoid hepatic first-pass metabolism and improve the oral bioavailability of administered drug; and to give rapid onset of action. This study aims to investigate the pain-modulating properties of beta-glucogallin sublingual tablet in the context of chronic

muscle inflammation through in vivo, in vitro, and computational analysis. The proposed sublingual tablet could offer a good approach to managing this type of pain. The anti-inflammatory and analgesic properties of beta-glucogallin could potentially help reduce pain and discomfort.

MATERIALS AND METHODS

Chemicals:

The BGG [(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl] 3,4,5-trihydroxybenzoate (Product code: G012; Lot. no.: T18D239) was purchased from Natural Remedies Pvt. Ltd., Bangalore. Purity of BGG was determined by the manufacturer by HPLC area normalization and was certified as 95.4%. Mannitol, MCC, Sodium alginate, Gellan gum, Ispaghula seed husk powder, Citric acid, Mg Stearate, Talc, microcrystalline cellulose (MCC) all from Loba Chem. (Mumbai, India).

Method:

I. Preformulation studies:

1. HPLC Chromatogram of BGG:

Shimadzu High Performance Liquid Chromatographic System LC 2010CHT with UV & PDA detector in combination with Class LC solution software used to determination of purity of BGG. ~10 mg sample was dissolved in 25 ml of water & injected (20µl) to HPLC. Purity was determined by area normalization as shown in figure 1.

II. Fabrication of sublingual tablets by direct compression method:

Sublingual tablets of BGG were prepared by direct compression. All ingredients were passed through a #80 mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of the 100 mg by direct compression method using 6-mm bi-concave punches on a Double Rotary Tablet Compression Machine (Rimek 10 station minipress). Batches F1-F9 were prepared by using three disintegrants for optimization of the disintegrant. Table No.1 summarizes the composition of BGG sublingual tablet formulations

III. Evaluation of sublingual tablets:

1. **Weight variation:** Ten tablets were weighed individually and then collectively, and the average weight of the tablets was calculated.
2. **Hardness:** The hardness of the tablets was determined by Monsanto hardness tester. A tablet hardness of about 3-4 kg is considered to be adequate for mechanical stability. Determinations were made in triplicate.
3. **Friability:** The tablets were tested for friability testing using Roche friabilator. For this test, six tablets were weighed and subjected to the combined effect of abrasion and shock in the plastic chamber of friabilator revolving at 25 rpm for 4 min and the tablets were then dusted and reweighed.
4. **In-vitro disintegration test:** In the USP (United States Pharmacopoeia) disintegration test for sublingual tablets, the disintegration apparatus for oral tablets is used without the covering plastic disks and 2 min is specified as the acceptable time limit for tablet disintegration fulfilling the official requirements.
5. **Drug content:** Tablets (n = 5) were weighed individually, and the drug was extracted in phosphate buffer (pH 6.8), and the solution was filtered by Whatman filter paper. Absorbance was measured at 217 nm after suitable dilution using a Shimadzu UV-1900i UV/Vis double-beam spectrophotometer.
6. **In-vitro drug release study:** Dissolution study was conducted for all formulations using USP dissolution rate test apparatus type-II (Labindia 8000). Five hundred milliliters of phosphate buffer (pH 6.8) was taken in a dissolution apparatus, which was maintained at 37°C ±0.5°C at 50 r.p.m. Ten-milliliters aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. Samples were collected at 2-min intervals and filtered by Whatman filter paperand analyzed spectrophotometrically at 217 nm.
7. **In-vitro permeation study:** *In-vitro* permeation studies were carried out with modified Franz's diffusion cells (D.K. Scientific, Ahmedabad, India). The medium used for these studies was phosphate buffer (pH 7.4), maintained at 37°C ± 0.5°C. Cellulose dialysis membrane was used as a permeation barrier. Samples were collected at predetermined time intervals (0, 5, 8, 15, 20, 30, 45, 60, 90 and 120 min). Samples were analyzed for drug content with a UV spectrophotometer set at 217 nm. All permeation studies were three replicates for F9 formulation.
8. **Stability studies of the optimized formulation:** Short Term Stability study was carried out according to ICH guidelines Q1C at 40°C ± 2 °C/75 ± 5% RH for 1 month for optimized batch P3. The optimized formulation sealed in aluminum foil was also kept at room temperature and humidity condition. At the end of studies, samples were analyzed for the % drug release and drug content.

IV. Evaluation of in vitro anti-inflammatory activity by Protein denaturation method[7]

The reaction mixture (10 mL) consisted of 0.4 mL of egg albumin (from fresh hen's egg), 5.6 mL of phosphate buffered saline (PBS, pH 6.4) and 4 mL of varying concentrations of *Phyllanthus fraternus* HE extract so that final concentrations become 25, 50, 100, 200, 400 and 800 µg/mL. Similar volume of double-distilled water served as control. Then the mixtures were incubated at (37^0c ±2) in a incubator for 15 min and then heated at 70^0 c for 5 min. After cooling, their absorbance was measured at 660 nm

(SHIMADZU, UV 1800) by using vehicle as blank and their viscosity was determined by using Ostwald viscometer. Diclofenac sodium at the final concentration of (25, 50, 100 & 200 µg/mL) was used as reference drug and treated similarly for determination of absorbance and viscosity. The percentage inhibition of protein denaturation was calculated by using the following formula,

% inhibition = 100 x (Vt / Vc - 1)

Where, Vt = absorbance of test sample, Vc = absorbance of control.

The extract/drug concentration for 50% inhibition (IC_{50}) was determined by plotting percentage inhibition with respect to control against treatment concentration.

Table 1: Composition of BGG sublingual tablet formulations

Ingredients	Formulation Batches (Quantity in mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	10	10	10	10	10	10	10	10	10
Mannitol	70	70	70	70	70	70	70	70	70
MCC (Microcrystalline cellulose)	15	13	11	15	13	11	15	13	11
Sodium alginate	2	4	6	-	-	-	-	-	-
Gellan gum	-	-	-	-	-	-	2	4	6
Ispaghula seed husk powder	-	-	-	2	4	6	-	-	-
Citric acid	2	2	2	2	2	2	2	2	2
Mg Stearate	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Talc	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75

Table 2: Evaluation parameters of batches F1-F9

Batch code	Average hardness (Kg/cm^2)	Disintegration time(s) n=6	Friability%	% drug content
F1	3.6	12.95± 0.011	0.60	97.34±0.281
F2	3.5	12.41± 0.020	0.49	98.10± 0.316
F3	3.2	11.50±0.030	0.42	98.25±0.389
F4	3.7	13.13±0.025	0.85	97.11±0.278
F5	3.8	14.95±0.026	0.79	97.98± 0.301
F6	3.9	16.30±0.081	0.82	98.40±0.321
F7	3.2	10.14±0.183	0.55	98.60±0.305
F8	3.1	9.54±0.330	0.40	98.80±0.200
F9	3.0	9.80±0.329	0.36	99.95±0.464

Table 3: Effect of Betaglucogallin on protein denaturation.

Treatment	Concentration (µg/ml)	% Inhibition of protein denaturation	Viscosity (cps)
Control	0	0	1.46
Betaglucogallin	25	27.128	0.69
	50	35.679	0.73
	100	98.862	0.78
Diclofenac sodium	25	28.741	0.57
	50	35.154	0.71
	100	111.11	0.84

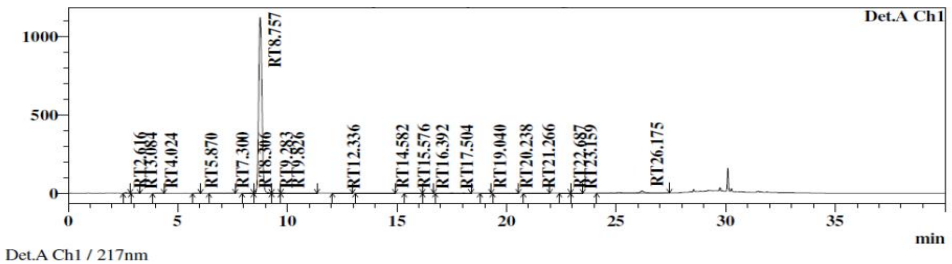

Figure 1: HPLC Chromatogram of BGG

RESULTS AND DISCUSSION

1. HPLC Chromatogram of BGG:

HPLC purity of BGG (By area normalization) was found to be 95.4 % Figure 1: HPLC Chromatogram of BGG.

2. Evaluation of sublingual tablets:

The prepared tablets were evaluated for weight variation, hardness, friability, drug content, in vitro disintegration time, in vitro dissolution, in vitro permeation studies. It was observed that all the tablets formulation passed the test for weight variation, as the percentage of weight variation was within the pharmacopeial limits. The prepared tablets in all formulations possessed good mechanical strength with sufficient hardness in the range of 3.0 to 3.9 kg/cm^2. Friability varied between 0.40% and 0.85%. Friability values less than 1% were an indication of good mechanical resistance of tablets. The drug content in all formulations was highly uniform and in the range of 97.34%-99.95%. The disintegration time of batch F9 was 9.80 s. Batch F9 showed the lowest disintegration time hence it was considered an optimized batch It was observed that formulation F9 containing 6% gellan gum as super-disintegrant showed faster disintegration rate as compared with other formulations. The results of the evaluation parameters of the sublingual tablets are depicted in Table 2. In vitro drug release of batch F9 was 100.1 % in 10 min. The % permeation of batch F9 containing 2% citric acid was 90.12. The in vitro release profile and in vitro permeation of batch F9is shown in Figures 2 and 3 respectively.

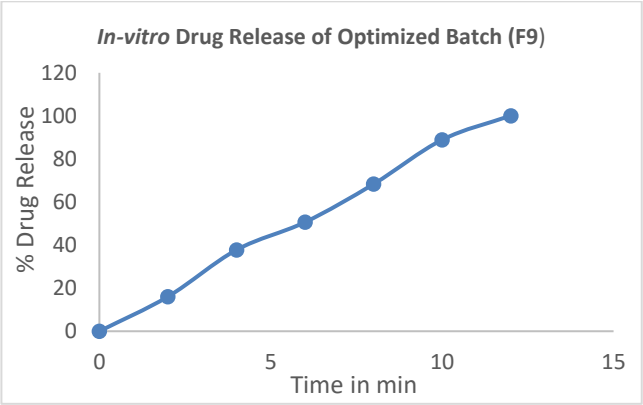

Figure 2: In-vitro Drug Release of Optimized Batch (F9)

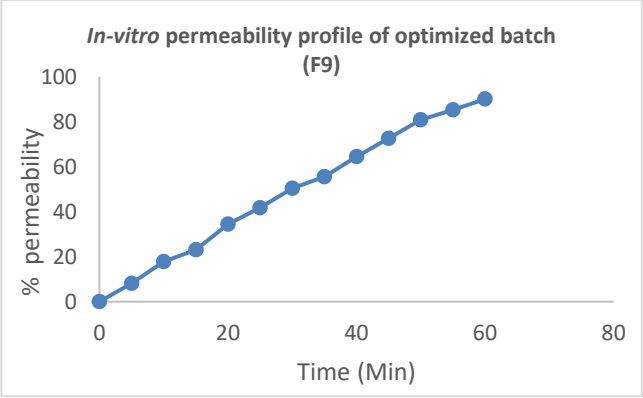

Figure 3: In-vitro permeability of Optimized Batch (F9)

The optimized formulation (batch F9) stored at 40 ± 2°C/75 ± 5% for 3 months. After storage at 40 ± 2°C/75 ± 5%, cumulative percentage drug release, disintegration time, hardness and % drug content were nearly similar to the initial results. Hence, it was clear that the drug and the formulation were thermally stable as well as not affected by the high humidity at 40 ± 2°C/75 ± 5%. Hence, we can conclude that formulation is stable.

3. Inhibition of protein denaturation

The inhibitory effects of different concentrations of Betaglucogallin on protein denaturation are summarized in Table 3. The present findings exhibited a concentration dependent inhibition of protein (albumin) denaturation by Betaglucogallin throughout the concentration range of 25 to 100 µg/mL. Diclofenac sodium was used as reference drug which also exhibited concentration dependent inhibition of protein denaturation. Betaglucogallin at concentration of 100 µg/ml showed significant inhibition of protein denaturation when compared with control. This was further confirmed by comparing their IC50 values. Betaglucogallin possessed IC50 value 52 µg/mL whereas that of diclofenac sodium was found to be 44 µg/mL.

Several anti-inflammatory drugs have shown dose dependent ability to inhibit thermally induced protein denaturation. It has been reported that one of the features of several non-steroidal anti-inflammatory drugs is their ability to stabilize (prevent denaturation) heat treated albumin at the physiological pH (pH, 6.2-6.5). This anti-denaturation effect was further supported by the change in viscosities. It has been reported that the viscosities of protein solutions increase on denaturation[7]. In the present study, the relatively high viscosity of control dispersion substantiated this fact. Ability of Betaglucogallin to bring down thermal denaturation of protein is possibly a contributing factor for its anti-inflammatory activity.

This study on sublingual Betaglucogallin tablets is of great significance due to the pressing need for more effective and rapid anti-inflammatory treatments. Inflammation is a common underlying factor in numerous chronic and acute diseases, necessitating the development of innovative therapies to address this issue.

The significance of this study lies in the formulation of a novel sublingual delivery system for Betaglucogallin, a natural anti-inflammatory compound. Sublingual administration offers several advantages, including rapid onset of action, bypassing first-pass metabolism, and enhanced patient compliance. If proven effective in clinical trials, these tablets may revolutionize the way inflammation is managed and treated.

By offering a potential alternative to conventional anti-inflammatory treatments, the sublingual Betaglucogallin tablets represent a significant step toward improving patient outcomes, reducing side effects, and providing a more patient-friendly approach to managing inflammation-related conditions. This research paves the way for further

investigations and the development of advanced anti-inflammatory therapies.

CONCLUSION

The formulation and evaluation of sublingual Betaglucogallin tablets have demonstrated their potential as a novel anti-inflammatory treatment. These tablets exhibit rapid disintegration and release profiles, ensuring immediate contact with the highly vascularized sublingual mucosa, leading to rapid absorption and onset of action. Furthermore, the sustained release of Betaglucogallin provides continuous therapeutic levels in the bloodstream over time. The sublingual delivery of Betaglucogallin may address the limitations of conventional anti-inflammatory treatments, such as the avoidance of first-pass metabolism, rapid relief of inflammation, and improved patient compliance. This study sets the stage for further preclinical and clinical investigations to confirm the efficacy and safety of sublingual Betaglucogallin tablets as a valuable addition to the arsenal of anti-inflammatory therapies.

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