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Research article

Formulation, development and in-vitro evaluation of a bambuterol hydrochloride in-situ gelling system for nasal delivery

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ABSTRACT

The goal of this project was to design, develop, and *in-vitro* evaluation of an in-situ gelling system for nasal administration of Bambuterol hydrochloride. All of the batches were prepared using different concentration of pectin, given different doses of simulated nasal electrolyte solution (SNES) i.e., 0.1 ml to 2.0 ml. All batches and formulation batches with a composition of 0.8 percent low methoxyl pectin underwent an in vitro gelation testing. The pH of the formulation reduced as the pectin content increased due to the acidic nature of pectin. The drug concentration was greater than 95%, and the apparent viscosity of the sol and gel was measured using a Brookfield viscometer (Rotational Viscometer Model). When the concentration of gelling polymer was increased from 0.5 to 1.0 percent, the gel strength (SOL) increased from 0.6 to 1 sec. The gel strength (GEL) increased from 0.7 to 13 seconds as a result of gelation. In vitro drug release experiments showed that the resulting formulations could release the medication for up to 10 hours when Higuchi kinetics were applied to all of them. The gels were stable across the six-month test period, according to the accelerated stability studies. There was no drug-polymer interaction, according to DSC and XRD analyses. Based on these findings, in situ nasal gel could be a possible drug delivery strategy for bambuterol hydrochloride, allowing it to bypass first-pass metabolism and hence improve bioavailability.

Keywords: Bambuterol hydrochloride, In-situ nasal gel, Controlled drug release, Gelling temperature, Stability studies

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INTRODUCTION

Since ancient times, mankind has been interested in the nasal route of medicine delivery. Nasal therapy, also known as Nasaya Karma, is a recognized kind of treatment in Indian medicine's Ayurvedic traditions [1]. The practice of administering locally active medicines intra nasally is older. In 1926, a scholarly paper regarding intranasal drug administration for local treatment showed how to improve nasal sinus irrigation. Many medications have been found in recent years to have a higher systemic bioavailability when self-medicated via the nasal route rather than oral administration. Some have been proven to replicate the plasma profile when given intravenously. Intranasal injection of vaccines, hormones, peptides and other medications has lately gained popularity as a systemic method of administration [2].

Intranasal medication delivery is now widely accepted and effective alternative to oral and parenteral administration. Intranasal administration of medications for symptomatic alleviation, prophylaxis, or treatment of topical nasal diseases has unquestionably been widely used for a long time[3]. Bambuterol hydrochloride is a long-acting adrenoceptor that is used to treat asthma. In the body, it is gradually transformed to Terbutaline, which is its active metabolite [4].

Nasal in-situ gelling inserts

The drug is embedded in a sponge-like hydrophilic polymer matrix, which is lyophilized to produce this solid dosage form. It allows for simple dosing with a high likelihood of systemic distribution while avoiding the severe conditions of the gastrointestinal tract and hepatic first-pass metabolism [5]. The polymer sponge absorbs water and forms a gel when it comes into contact with the highly vascularized nasal mucosa, from which the pharmaceutically active substance is released in a controlled manner. For extended-release applications, the inclusion of bio-adhesive polymers ensures a longer nasal residence period [6].

MATERIALS AND METHOD

Bambuterol hydrochloride was obtained from Meditab laboratories, Satara. Low methoxyl Pectin was obtained from Krishna Pectins, Jalgaon. Research Lab fine chem in Mumbai provided the potassium dihydrogen phosphate.

Method of preparation of in situ gel of Low Methoxyl Pectin

A precisely weighed quantity of Low Methoxyl Pectin (0.5–1.0 percent w/v) was disseminated in distilled water with scattered calcium carbonate. A magnetic stirrer was used to agitate the dispersions for 20 minutes at room temperature. Simultaneously, benzalkonium chloride (0.002 % w/v) was added. Finally, with stirring, Bambuterol hydrochloride was added. All of the formulations had a pH of 4.5 to 6.5. Glass vials were filled with the formulations, which were then sealed with aluminum caps and rubber closures. The formulations were kept in the refrigerator (4º-8^0 Celsius) until they were used [7, 8].

The preliminary results for formulation batches prepared at 1.0 to 2.0 percent showed that the gel formed had a higher viscosity, which would influence dripping, so the next trials were conducted using lower pectin concentrations. The critical cation concentration, in vitro gelation, pH, viscosity, gel strength, drug content homogeneity, and in vitro drug release research of the created preliminary batches of in-situ gels were all evaluated.

Selection of Optimized batch

The optimum batch was chosen based on the required properties of in-situ gel, including immediate gelation for an extended period (+ +), optimum viscosity for spraying as a droplet, pH in the nasal cavity range, satisfactory gel strength, and good drug release behavior in the diffusion media used in the study [9-11].

Evaluation of optimized batch

An optimized batch selected was further evaluated for following tests to confirm its performance characteristics.

A. Water holding capacity

Low Methoxyl Pectin that has been optimized in a pre-weighed centrifuge tube; pectin formulation was combined with 1 ml SNES for gelation. The weight of the gels is represented by W_0. The gels were centrifuged for 10 minutes at 15,000 rpm. Filter paper was used to remove the water seepage. The gel was reweighed to calculate the weight of retained water (W). W/W_0 X 100 % is the water holding capacity of the gels [12].

B. Expansion coefficient

Expansion of the formulation into gel after transition may cause undesirable effects or irritation into nose. So, the formulation should have good optimum or no expansion effects [13].

Method

1:1 volume of formulation to SNES was taken and allowed for transition into gel and the volume was noted (V_m). Then, more 2 ml of SNES was added and volume was noted (V_1). Volume of gel after transition was calculated ($V_G = V_M - V_1$). The expansion coefficient was calculated as follows:

$$S(\%) = \frac{V_M - V_1}{V_M} \times 100 \quad \frac{V_G}{V_M} \times 100$$

C. *In-vitro* drug release

In a Franz diffusion cell with a membrane for dialysis, drug release for the improved batch was tested in-vitro (cut-off 12,000-14,000 k Da).To construct the fake membrane, pieces of dialysis membrane were soaked in phosphate buffer (PB) pH 7.4 for 24 hours before mounting on the diffusion cell. After a 20-minute pre-incubation period, 2 ml of the optimized formulation (E4-0.5ml SNES) was poured into the donor compartment, while PB pH 7.4 was placed in the receptor compartment. To cause gelation, SNES was used. The temperature of the receptor compartment was maintained at 37± 1ºCelsius throughout the experiment. At predefined intervals, the required number of samples was collected from the receptor compartment, and the sampled volume was replenished with PB pH 7.4. The samples were diluted appropriately and examined using a UV visible spectrophotometer set at 279 nm [14].

D. Stability study of Optimized batch

Stability testing is used to determine a re-test period for a drug substance or a shelf life for a drug product, as well as recommended storage conditions, and to provide evidence on how the quality of a drug substance or drug product changes over time as a result of various environmental factors such as temperature, humidity, and light. (ICH Q1A (R2) guideline) [15].

In-situ gel compositions were subjected to stability testing in accordance with ICH (International Conference on Harmonization) guidelines [16]. An appropriate amount of in-situ gel was stored in amber-colored sealed vials in desiccators containing a saturated sodium chloride solution at a relative humidity of 75.5 percent. At the conclusion of the first, second, and third months, samples were taken from the desiccators, which was placed in a hot air oven set to 40°C [17]. The gel's physical stability was examined for turbidity and gelation on a regular basis. At predetermined time intervals, clarity, drug content, in vitro gelation, viscosity of sol/gel state, gel strength, pH, and in- vitro drug release were all examined [18].

RESULT AND DISCUSSION

The pre-formulation study, identification and characterization, organoleptic characterization of drug Bambuterol hydrochloride was carried out. Among the results obtained for prototype formulations, optimization was done and the optimized formulation was evaluated. The optimized batch was concluded from parameters such as Critical Cation Concentration, *In- vitro* gelation study, pH, viscosity, gel strength, drug content uniformity, *in- vitro* drug permeation study as depicted in Table 1. The optimized batch selected was further evaluated for tests to confirm its performance

characteristics such as water holding capacity (Table 2), expansion coefficient (Table 3), *in-vitro* drug release (Table 4), stability study (Table 5).

A. Water holding capacity

As shown in Table 2, the optimized formulation can hold **92.46 %** of water even at higher stress conditions. Therefore, there are very less chances of seepage of water out of the gel at the site of delivery after transition**.**

B. Expansion coefficient

As shown in Table 3, the optimized formulation has only 10.75% expansion coefficient. Individuals may not experience discomfort if in-situ gel is injected into the nasal cavity.

C. Study of drug release in vitro

As shown in Table 4 *In-vitro* testing was performed on the optimized batch (E4) using a Franz diffusion cell with phosphate buffer pH 7.4 in the receptor compartment. The formulation showed 96.18 percent drug release in 12 hours, indicating that it has a long-term release property (Figure 1).

Table 1: Conclusions of the optimization studies
(For optimized batch E4)

Weight before centrifugation, W_0 (gm)	Weight after centrifugation, W (gm)	Water holding capacity, S_0=W/W_0.10	Average Water holding capacity (%)
1.067	0.982	92.03	92.46 ± 0.428%
1.067	0.988	92.59	
1.067	0.990	92.78	

Table 2: Water holding capacity of the formulation

Initial volume, V_M (mL)	Volume of gel + additional 2 mL ANF, V_1	Volume of gel, $V_G = V_1 - 2$		S %	Average S%
2	4.15	2.15	10.75	10.83+ 0.22	
2	4.15	2.15	10.75		
2	4.2	2.2	11		

Table 3: The optimized formulation's expansion coefficient

Study	Result	Conclusion
Critical Cation Concentration (CCC)	0.5 mL of SNES, i.e., 0.5: 1 to the formulation	Which mimics the available natural nasal fluid quantity in nasal cavity
In-vitro gelation study	++ (Immediate gelation with no drip property)	Shows desired gel property
pH	4.56	Should be 4.5-6.5, can be adjusted by addition of NaOH.
Viscosity	Before: 30 cps After: 460 cps	Optimum viscosity, Shows transition to stiff gel.
Gel strength	10.67 s	Standard: 10-50 s
Drug content uniformity	99.66 %	
In vitro drug permeation study	After 12 h 96.02 %	Almost 96% release within 12h, Good sustained release.

Table 4: The optimized formulation's in vitro drug release profile

Time (h)	% Cumulative Drug Release
0	0
1	18.91 ± 0.396
2	29.49 ± 2.253
3	35.91 ± 2.547
4	47.31 ± 1.069
5	52.68 ± 0.417
6	62.46 ± 1.264
7	65.53 ± 0.579
8	71.78 ± 0.604
9	83.53 ± 0.845
10	88.22 ± 0.898
11	92.05 ± 0.522
12	96.18 ± 0.215

Figure 1: In vitro drug release profile of formulations E1 to E6

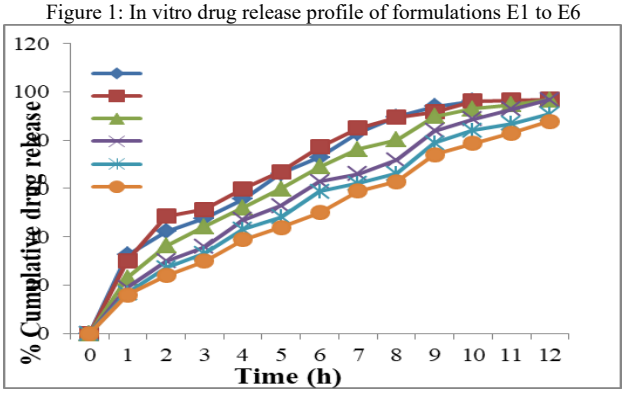

Table 5: Stability study of optimized formulation at 40 ± 2^{0}C and 75 ± 5% RH

Period	Evaluation Parameters*								
	Physical properties	In- vitro gelation	Viscosity(cp)		pH	Drug content (%)	% CDR (After 14 h)	Gel strength (s)	
			Sol	Gel	*NA*	*NA*	*NA*	Sol	Gel
0 Month	No gelation	++	30	464	4.91 ± 0.01	99.3 ± 0.524	96.66 ± 0.139	0.98 ± 0.05	20.48 ± 2.64
1 Month	No change	No change	30	462.2	4.84± 0.02	98.94 ± 0.069	96.04 ± 0.06	0.94 ± 0.024	19.06 ± 1.87
2 Month	No change	No change	30	460	4.82± 0.005	98.1 ± 0.375	95.63 ± 0.173	0.89 ± 0.022	18.66 ± 1.589
3 Month	No change	No change	30	460	4.74 ± 0.005	97.64 ± 0.259	95.36 ± 0.157	0.87 ± 0.0172	17.3 ± 0.564

* n = 3; mean + standard deviation

CONCLUSION

It can be concluded based on the findings of this study that:

- The drug and the excipients had no significant interactions, indicating that the drug was compatible with the excipients used in formulation development.
- Initially 2 percent Low Methoxyl Pectin showed optimum gelation.
- An alternative approach- the use of Calcium carbonateas a novel calcium ion reservoir was developed and optimized (0.005 percent), which helps to reduce amount of Low Methoxyl Pectin in the formulation from 2 percent to 1 percent.
- Prototype formulations were made by adjusting the concentration of Low Methoxyl Pectin (1.0 percent to 2.0 percent), however the findings showed that the gel generated

had a higher viscosity, which would impair dripping, so the next trials were done with lower pectin concentrations.

- Batch D4 (0.8 percent Low Methoxyl Pectin) showed optimal gelation, pH in the nasal cavity range, acceptable viscosity for droplet spraying (Sol 30 cps and gel 460 cps), optimum gel strength (Sol 0.72 s and gel 10.67 s), drug content within limit 99.66 percent, and increased drug release (96.02 percent within 12 h).
- The optimized formulation (batch D4) was next tested in vitro for drug release, and all of these tests validated the in-situ gel's good performance features.
- Optimized formulation was also retained stability at accelerated condition for period of 3 months.

As a result, all of the production and performance characteristics have been confirmed, resulting in an optimized and stable in situ gelling system for bambuterol hydrochloride intranasal delivery.

Finally, the in-situ gel method can be used for needleless administration, potentially leading to the development of a patient-friendly medication delivery system. It has the potential to extend the time the formulation spends in the nasal cavity. As a result, in situ gel for nasal distribution is a potential option to other routes of administration for improving bambuterol hydrochloride therapeutic efficacy.

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