DESIGN OF MEDICATED LOZENGES FOR PEDIATRICS

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ABSTRACT

Montelukast sodium was formulated as a oral retentive lozenge for the treatment of asthma in pediatric patients. There are dosage forms like syrups, tablets in the market but still there is a need for new dosage form which acts effectively. So the present investigation prepared and evaluated lozenges of Montelukast sodium using hydroxy propyl methyl cellulose as polymer different concentrations to increase retention time. Among the 3 formulations, formulation F2 containing 0.5% hydroxy propyl methyl cellulose was found to be promising. This formulation exhibited an in vitro drug release of 69.24% in 30 mins. The benefits of these prepared lozenges are increased bioavailability, reduction in gastric irritation by-passing first pass metabolism. The sucrose based lozenges were prepared by heating and congealing method in a candy based industry on request. All the formulations prepared were subjected to various physico-chemical parameters like hardness, content uniformity, friability, weight variation, moisture content etc. The prepared formulations have a hardness of 10-12 Kg/cm², free from gritty particles. All the formulations were tested for drug excipient interactions subjecting to IR Spectral analysis. In vitro drug dissolution studies showed 69.24% for F2, 64.01% for F3 release of drug in 30 min, 97.31% in 10 minutes from F1 formulation. The lozenges will provide an attractive alternative formulation in the treatment of asthma in pediatric patients. Short-term stability studies on the promising and other formulations indicated that there were no significant changes in the drug content and in vitro dissolution characteristics. IR spectroscopic studies indicated that there were no drug-excipient interactions. The prepared lozenges of Montelukast sodium could stay in the mouth for a longer period of time, which indicates a potential use of lozenges of Montelukast sodium for treating asthma.

Key words: Montelukast sodium; Lozenges; Pediatrics.

Introduction

Asthma is characterized by episodic reversible bronchospasm resulting from an exaggerated bronchoconstrictor response to various stimuli. The basis of bronchial hyperactivity is not entirely clear, but it is widely believed to result from persistence bronchial inflammation. Hence, bronchial asthma is best considering a chronic inflammatory disorder of the airways that cause recurrent episodic of wheezing breathlessness, chest tightness, coughing experienced by the patient with asthma. Particularly at night and early morning, is usually associated airflow obstruction. This common disease affects about 5% of adults and 7% to 10% of children.1,2

Leukotrienes cause bronchoconstriction, oedema, and mucus secretion in models of asthma and are produced in excess quantities in asthmatic patients. Leukotriene receptor antagonists and biosynthesis inhibitors have been produced to improve the signs and symptoms of asthma. Leukotrienes appear to play an important role in the inflammatory process of asthma and number of drugs may modify this action. Leukotriene modifiers (receptor antagonist and biosynthesis inhibitor) represent the first mediator specific therapeutic option for asthma Zileuton
prevents leukotrienes synthesis by inhibiting 5-lipoxygenase, while leukotriene antagonist such as zafirlukast, montelukast, pranlukast may be used to block specific receptor. Leukotriene modifier has significant additive benefits in the management of patients who suffer from mild to moderate asthma and who are inadequately controlled on inhaled corticosteroid therapy. Montelukast has a beneficial effects in exercise induced asthma and aspirin sensitive asthma. Judicious use of montelukast based on available scientific evidences is warranted in pediatric asthma management for optimal control of asthma symptom score and prevention of deterioration of lung function. Several cases of eosinophilic conditions including fulminant eosinophilic endomyocarditis, Churg-Strauss syndrome, have been reported in association with the use of cysteinyl leukotriene receptor antagonists, including zafirlukast, montelukast, and pranlukast, in asthmatic patients. Montelukast sodium was formulated as a oral retentive lozenges for the treatment of asthma in pediatric patients. There are dosage forms like syrups, tablets in the market but still there is a need for new dosage form which acts effectively and locally. So the present investigation aims to design, prepare and evaluate lozenges of Montelukast sodium using polymers with different concentrations.

**Materials and Methods**

Montelukast sodium was gift sample from Ajanta Pharmaceuticals, Mumbai. Liquid glucose from Rakesh chemicals Pvt. Ltd., Mumbai. Hydroxy propyl methyl cellulose from Himedia Laboratories Ltd., Mumbai and Sucrose SD Fine Chemicals, Mumbai. All other chemicals used were of analytical grade.

**Plan of work:**

Three formulations of Montelukast sodium medicated lozenges containing with and without mucoadhesive polymers

**Phase-I Studies: Preparation of medicated lozenges**

It was planned to prepare candy based lozenges by heating and congealing method using Hydroxy Propyl Methyl Cellulose as polymer

**Step-1:** The desired quantity of sugar was dissolved in water by heating and stirring in a copper kettle until sugar was completely dissolved. Corn syrup was added when the cooking temperature reaches 110ºC. Cooking was then continued to 145 - 156ºC till the syrupy base becomes thick.

**Step-2:** The finished cooked syrup (154.4ºC) was then placed in vacuum chamber which was maintained at 274 mm Hg for about 30 minutes to remove the traces of water molecules and to give plasticity to the base prepared.

**Step-3:** The candy base was then transferred to a water-jacketed stainless steel cooling table of 214 ft. for the mixing operation. This mixing was done manually. During the mixing cycle, the temperature of candy base (154ºC) was brought to 90ºC to form a solidified mass. A hydrogenated vegetable oil-based lubricant was spread onto the table surface to alleviate this condition. At this stage the Drug, mucoadhesive polymers, citric acid, other excipients such as Colour and flavoring agents were added manually and mixed thoroughly.

**Step-4:** Then this solidified mass was placed between the rollers of the batch former. The rollers move in a counter rotating pattern that rolls the batch backward and forward so as not to distort any portion of the solidified mass in the batch former to form a rope size in shape. The diameter of the mass rope as it leaves the lower end of the former is adjusted by a hand wheel. The thickness of the rope was determined by the diameter of the size rollers and the gap between rollers.

**Step-5:** The candy rope is fed into a final set of sizing rollers was discharged from the batch former and rope sizer and from there into the rotating dies head furnished with plungers and guiding cams for the stamping and formation of the individual lozenges.

**Step-6:** Hot air was blown over the product (Lozenges) in the drying chamber which was rotated at a temperature of 15-20ºC, at a velocity of 1500-3000 ft/mins as the lozenges passed from the cooling belts. Then the dried Lozenges is then taken in other container and lubricated with oils so that prepared Lozenges should not stick to each other.
Step-7: The prepared lozenges were packed with the help of machine called Maksom Double Twist Wrapper.

Phase-II Studies: Characterization of prepared medicated lozenges.

The formulated lozenges will be subjected for

a) Weight variation, b) Hardness, c) Drug content uniformity, d) Thickness, e) Diameter, f) Moisture content studies

Phase-III: Stability studies:

Stability studies were also carried out at 30°C with 65% RH and 40°C with 75% RH for the period of six months. Drug content estimation was carried during intervals of 15 days.

Phase-IV Drug excipient interaction studies:

All the formulations will be subjected for IR analytical techniques.

Phase-V: In-vitro drug release studies:

All the formulation prepared to subjected for in-vitro drug release studies at the salivary pH conditions (6.4) using reported modified USP dissolution method.

USP XXIII Dissolution test apparatus was used by taking 100 ml of pH 6.4 buffer in 250 ml beaker lozenge was placed in it, rotating paddle at a speed of 50 rpm and temperature 37±1°C was maintained. 5 ml aliquots were withdrawn at 5, 10, 15, 20, 25 and 30 minutes intervals, after each withdrawal of a sample an equal volume of dissolution medium was added to the dissolution vessel. The filtered samples were diluted and analyzed spectrophotometrically at 346.0 nm.

Phase-VI: Oral mucosal irritation test:

It will be performed primarily by examining each volunteer oral cavity barely with naked eyes using focus and lens to notice of any changes in tissues after the usage of formulations. Then photographic image of oral cavity of human volunteers will be taken after subsequent application for 72 hrs i.e., at completion of study period and these images will be compared to determine the difference with the images taken at 0 hour of study i.e., prior to first usage of formulation. Moreover, mucosal irritation will be evaluated by questioning the human volunteers at regular interval of time about the feeling of irritancy, which appears to be highly subjective for the study. Finally, the oral mucosal skin irritancy will be evaluated for any changes like oral erythema, inflammation, redness, haemorrhagic lesions or acute painful ulcers (cancer sores).

RESULTS AND DISCUSSION

Montelukast sodium Lozenges:

Montelukast sodium was the drug of choice for the treatment of asthma and fever. In the present work Hydroxy Propyl Methyl Cellulose selected as polymers with different The formulation F₁ was without added hydrocolloid and evaluated for the utility in the treatment.

Phase-I Studies: The prepared lozenges were orange flavoured spherical in shape, 2 gms in weight and 17 mm diameter and light orange in colour.

Phase-II Studies: Physico-chemical properties of prepared tablet lozenges:

- **Hardness Studies:** As shown in Table No-2 the hardness of the lozenges prepared were 10.84 without hydrocolloids, 11.0 with HPMC 0.5%, 10.85 with HPMC 1%, in Kg/cm² respectively.

- **Weight Variation:** As shown in the table no-2 the weight variation of the lozenges was not more than 5%

- **Drug Content:** As shown in the table No-2 the drug content of the lozenge was within 95 to 105%.

- **Thickness:** As shown in Table No-2 the thickness of the lozenges prepared were 3.30 without hydrocolloids, 3.30 with HPMC 0.5%, 3.27 with HPMC 1%, in mm respectively.

- **Diameter:** As shown in Table No-2 the diameter of the lozenges prepared were 20.00 without hydrocolloids, 20.03 with HPMC 0.5%, 20.23 with HPMC 1%, in mm respectively.

- **Moisture content:** As shown in the table no-2 the moisture content of the lozenges was within 2%.
Phase-III Studies:

- **Stability studies:** The stability studies showed that there was no considerable change in hardness, weight, thickness and drug content.

Phase-IV Studies:

**Infra-red spectrophotometric analysis for drug-excipient interactions:**

Drug excipient interactions were ruled out in the promising formulations Montelukast sodium by IR spectroscopic studies using KBr pellet method.

Pure drug Montelukast sodium has exhibited IR spectrum indicating the presence of hydroxylic group in carboxylic acid & hydroxyl group present in tertiary carbon. Hence it has exhibited a broad band around 3411 cm$^{-1}$ indicating overlapping of these peaks. The peak due to the C-H peaks has appeared as shoulder between 2900 cm$^{-1}$ to 3100 cm$^{-1}$. The C=O peak has appeared at 1636 cm$^{-1}$ along with a merged peak at 1613 cm$^{-1}$. Methylene groups have a characteristic bending absorption of approximately 1402 cm$^{-1}$This is due to the complex structure of the drug molecule.

Formulation F$_2$: Drug and hydroxy propyl methyl cellulose (0.5%) are used. Methylene group have a characteristic bending absorption of approximately 1375 cm$^{-1}$.These observations suggested that drug has not undergone any chemical reaction.

Formulation F$_3$: Drug and hydroxy propyl methyl cellulose 1% are used. Methylene group have a characteristic bending absorption of approximately 1375 cm$^{-1}$.These observations suggested that drug has not undergone any chemical reaction.

Phase-V: **In-vitro Drug Dissolution Studies**

- **Without added hydrocolloid (F$_1$):** The drug dissolution studies indicated that in 10 minutes time 96.30% of the drug was dissolved. (Table No 3).

- **With added Hydroxy Propyl Methyl Cellulose 0.5% (F$_2$):** The drug dissolution studies indicated that in 30 minutes time 69.24% of the drug was dissolved. (Table No 3).

- **With added Hydroxy Propyl Methyl Cellulose 1% (F$_3$):** The drug dissolution studies indicated that in 30 minutes time 64.01% of the drug was dissolved. (Table No 3).

Phase-VI: **Oral mucosal irritation test**

Results of in-vivo studies in human volunteers under the supervision of qualified team of pediatricians revealed that no redness or ulcer formation or any irritation on oral mucosa was observed. Hence, the formulations prepared were concluded to be free from oral mucosal irritations. (FIG No.4).

**CONCLUSION**

Following conclusions can be drawn from the results obtained in the present investigation:

- The physico-chemical characterization revealed that all the formulations were found to show acceptable thickness, weight and hardness.

- Addition of hydrophilic mucoadhesive polymer Hydroxy Propyl Methyl Cellulose, yield good results to prolong dissolution time and the drug release in salivary pH conditions for a period of 30 minutes.

- Hydroxy Propyl Methyl Cellulose (0.5%) was found to be suitable in prolongation of dissolution of tablet lozenges for a period of 30 minutes.

- The drug content estimation showed uniform drug content in all the formulations.

- The moisture content test reveals that the prepared formulations were within the limits.

- IR spectroscopic studies indicated that there were no drug-excipient interactions.

- The stability studies proved that the prepared lozenges were found to be stable when stored at air tight containers or twist strips at 30±2°C & 65% RH and 40±2°C & 75% RH.

- Results of in vivo studies in human volunteers under the supervision of qualified
team of pediatricians revealed that no redness or ulcer formation or any irritation on oral mucosa was observed. Hence, the formulations prepared were compatible to be used as drug delivery.

The present work “development of medicated lozenges” are of industrial interest, as these offer patient convenience, improved compliance and comfortness to the patients in effective treatment.

Further studies like bioavailability and long term stability study to assess the shelf-life need to be continued to exploit them as alternative products to the conventional swallowable tablets/capsules.

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- We are very much thankful to chairman MKU- Kenya.

Table-1: Working formulae to prepare tablet lozenges

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Ingredient</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>F₁</td>
</tr>
<tr>
<td>1</td>
<td>Sugar</td>
<td>690 gms</td>
</tr>
<tr>
<td>2</td>
<td>Liquid glucose</td>
<td>291 gms</td>
</tr>
<tr>
<td>3</td>
<td>Drug</td>
<td>2 gms</td>
</tr>
<tr>
<td>4</td>
<td>Hydroxy Propyl Methyl Cellulose</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Citric Acid</td>
<td>10 gms</td>
</tr>
<tr>
<td>6</td>
<td>Flavoring Agent</td>
<td>6.7 gms</td>
</tr>
<tr>
<td>7</td>
<td>Colouring Agent</td>
<td>0.3 gms</td>
</tr>
<tr>
<td></td>
<td>Total Weight</td>
<td>1000 gms</td>
</tr>
</tbody>
</table>

* Each tablet lozenges contains 4 mg of Drug.
* Each tablet lozenges contains weight of 2 gms.

Table-2 Physico-chemical parameters of prepared montelukast sodium lozenges

<table>
<thead>
<tr>
<th>Sl.No</th>
<th>Parameter</th>
<th>Standard Limit</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>F₁</td>
</tr>
<tr>
<td>1</td>
<td>Hardness test (Kg/cm²)</td>
<td>---</td>
<td>10.84±0.73</td>
</tr>
<tr>
<td>2</td>
<td>Weight Variation (gm)</td>
<td>&gt;250mg-5%</td>
<td>2.03±0.02</td>
</tr>
<tr>
<td>3</td>
<td>Thickness (mm)</td>
<td>--</td>
<td>3.3±0.15</td>
</tr>
<tr>
<td>4</td>
<td>Drug Content (%)</td>
<td>90-110%</td>
<td>96.035±1.58</td>
</tr>
<tr>
<td>5</td>
<td>Diameter (mm)</td>
<td>--</td>
<td>20.0±0.53</td>
</tr>
<tr>
<td>6</td>
<td>Moisture Content (%)</td>
<td>2%</td>
<td>1.95±0.19</td>
</tr>
</tbody>
</table>

* Each reading is a mean of three replicates.
* Each lozenge contains 4 mg of Montelukast sodium
| S.I.NO | Time (min) | Square root of time | Log time | F1 | F2 | F3 |
|-------|------------|---------------------|----------|------------------|------------------|------------------|------------------|------------------|------------------|
|       |            |                     |          | % Cumulative amt of drug release ± SD. | % Cumulative amt of drug remaining | % Cumulative amt of drug release ± SD. | % Cumulative amt of drug remaining | % Cumulative amt of drug release ± SD. | % Cumulative amt of drug remaining |
|       |            |                     |          | % Cumulative amt of drug release ± SD. | % Cumulative amt of drug remaining | % Cumulative amt of drug release ± SD. | % Cumulative amt of drug remaining | % Cumulative amt of drug release ± SD. | % Cumulative amt of drug remaining |
| 1     | 0          | 0                   | 0        | 0                       | 0                       | 0                       | 0                       | 0                       | 0                       |
| 2     | 05         | 2.24                | 0.35     | 62.17±0.08               | 37.83                   | 19.05±0.15               | 80.95                   | 17.03±0.22               | 82.97                   |
| 3     | 10         | 3.16                | 0.50     | 96.30±0.44               | 3.70                    | 37.21±0.23               | 62.79                   | 35.23±0.49               | 64.77                   |
| 4     | 15         | 3.87                | 0.59     | ---                     | ---                     | 47.89±0.30               | 52.11                   | 45.21±0.45               | 54.79                   |
| 5     | 20         | 4.47                | 0.65     | ---                     | ---                     | 52.59±0.42               | 47.41                   | 50.24±0.56               | 49.76                   |
| 6     | 25         | 5.00                | 0.70     | ---                     | ---                     | 61.20±0.31               | 38.80                   | 57.08±0.47               | 42.92                   |
| 7     | 30         | 5.48                | 0.74     | ---                     | ---                     | 69.24±0.15               | 30.76                   | 64.01±0.34               | 35.99                   |

Table-3 *In vitro* drug release data

* Each reading is a mean of three replicates.

* Each lozenge contains 4 mg of Montelukast sodium
Figure-1: Comparative studies of Montelukast sodium lozenges with and without hydrocolloids (F₂, F₃)

![Graph showing comparative drug release](image)

Figure -2: IR spectrum of Montelukast sodium

![IR spectrum graph](image)
Figure-3: IR Spectrum of F2

Figure-4: IR Spectrum of F3

Figure-5
GLIMPSES OF SKIN IRRITATION TEST OF ORAL MUCOSA IN HEALTHY HUMAN VOLUNTEERS

0 hr

0 hr

0 hr

24 hrs

24 hrs

24 hrs

48 hrs

48 hrs

48 hrs

72 hrs
Male

72 hrs
Male

72 hrs
Female
References.


