Some Variables Affecting the Formulation of Oral Loratadine Suspension

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Abstract

Loratadine is a long acting non-sedating anti-histaminic agent that was developed for the treatment of seasonal allergic rhinitis, whose anti-histaminic action is more effective than the other anti-histaminic drugs available commercially. This project was carried out to prepare an acceptable suspension through studying the release of drug in presence of different types and concentrations of suspending agents such as polysorbate 80, xanthan gum, sodium carboxymethylcellulose (NaCMC), aluminum magnesium silicate (veegum) and sodium alginate. The effects of these suspending agents were studied at pH 1.2 (0.1N HCl) and 37°C. The results showed that the release rate of loratadine in the presence of these suspending agents was dependent on their types and concentrations. The results showed that loratadine release from the formula prepared from xanthan gum is more than that prepared from other polymers in the following order: Sodium alginate < NaCMC < veegum ≤ xanthan gum. However, elegance of suspension was better on using xanthan gum in a concentration of 0.5%. The obtained results were utilized to formulate 0.1% suspension of loratadine which is physically stable with an optimum drug release. The rheology, sedimentation volume, resuspendability and expiration date were evaluated for the selected formula. The formula that contains loratadine, xanthan gum, glycerol, sorbitol, methyl paraben, propyl paraben, sodium edetate, raspberry flavor at pH 5.0 appears to be a promised formula to be present with estimated shelf life of about 3.8 years.

Key word: loratadine, suspension, suspending agent, xanthan gum.

Introduction

A coarse suspension is a dispersion of finely divided, insoluble solid particles (the dispersed phase) in a fluid (dispersion medium or continuous phase) (1). A conventional suspension may be readily prepared in an aqueous solution with small percentage of hydrophilic polymers (like methyl cellulose, hydroxypropylcellulose and xanthan gum), as well as small percentage of surfactant like polysorbate 80. The suspending agent was used to achieve homogeneity of redispersed suspension while surfactants are used for wetting and dispersing of insoluble particles (2). For many patients, the liquid dosage form is preferred over the solid dosage form of the same drug because of the ease of swallowing liquids and flexibility in the administration. The disadvantage of disagreeable taste of certain drugs (loratadine bitter taste) is overcome when the drug is administered as undissolved particles (3). In general, aqueous suspension gives more extended effect than aqueous solution (4). Insoluble or poorly soluble drugs in suitable solvents could be formulated as flavored suspension as an ideal choice, example; nalidixic acid suspension (5) and fluconazole suspension (6).
Commercially available loratadine solution (syrup) products contain excipients that are inappropriate for pediatric population, particularly the neonatal and infant age groups. To improve the solubility of loratadine, most of the syrups contain propylene glycol which may put the infants at risk of displacement of bilirubin and consequently hyperbilirubinemia. Excessive intake of propylene glycol and subsequent metabolism to lactic acid may cause the development of hyperosmolality and lactic acidosis.

Loratadine is a tricyclic antihistamine, which has a selective and peripheral H₁-antagonist action. It has a long-lasting effect and does not normally cause drowsiness because it does not readily enter the cerebro spinal fluid (CSF). It is white to off-white powder, practically insoluble in water, but very soluble in acetone, alcohol and chloroform. Loratadine rapidly absorbed after administration, peak plasma concentration being attained in about 1 hour. It is extensively metabolized; the major metabolite is desloratadine, which has potent antihistamine activity. The elimination $t_{1/2}$ of loratadine and desloratadine are 8.4 and 28 hours respectively.

Chemical formula: $C_{22}H_{23}ClN_2O_2$
Mol. wt: 382.8 gm
Melting point: 134-136 C

There are different types of suspending agents used in suspension can be classified as:

1. Naturally occurring suspending agents like xanthan gum, sodium alginate, that forms multilayer film around the drug particles.
2. Semi synthetic suspending agents like NaCMC, which form multilayer also.
3. Synthetic suspending agents (surfactants) like polysorbate 40 (tween 40), that form monomolecular film.
4. Finely divided solids like veegum which form solid particle film.

The goal of this study is to formulate the loratadine as a suspension instead of syrup to mask its bitter taste, to improve its stability and to decrease side effects of the excipient by decreasing their use in the suspension formula.

**Experimental**

**Materials and Equipments**


**Method of Preparation**

**Preparation of stock dispersion of suspending agents:**

Stock dispersion of each suspending agent used (polysorbate 40, xanthan gum, NaCMC, veegum and sodium alginate) was prepared by dispersing (10, 1, 1.5, 5 and 3 gm) of the suspending agents, respectively in 75 ml of distilled water (D.W) using an electrical mixer at 150 r.p.m. The volume of the dispersion was made up to 100 ml with D.W, the resultant dispersions were allowed to hydrate for 24 hours.

**Preparation of suspension:**

Loratadine suspension was prepared by levigating 0.1 gm loratadine in a mortar with the prepared dispersion of suspending agent. When smooth paste was formed, the remaining of the vehicle was added and the volume completed to 100 ml with shaking.

**Effect of type and concentration of suspending agent on the drug release:**

The dissolution pattern of loratadine was studied in the presence of different types and concentrations of suspending agents including: polysorbate 40, xanthan gum, NaCMC, veegum and sodium alginate.

**Formulation of loratadine suspension:**

Five different formulas were prepared using different suspending agents as shown in table (1)
Table (1): Different formulations of loratadine as suspension dosage form represented as % (w/v)

<table>
<thead>
<tr>
<th>Materials</th>
<th>Formula number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Loratadine</td>
<td>0.1</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>0.5</td>
</tr>
<tr>
<td>SCMC</td>
<td>0.5</td>
</tr>
<tr>
<td>Veegum</td>
<td>2</td>
</tr>
<tr>
<td>Polysorbate 40</td>
<td></td>
</tr>
<tr>
<td>Methyl paraben</td>
<td></td>
</tr>
<tr>
<td>Propyl paraben</td>
<td></td>
</tr>
<tr>
<td>Glycerol</td>
<td></td>
</tr>
<tr>
<td>Sorbitol</td>
<td></td>
</tr>
<tr>
<td>Disodium edetate</td>
<td></td>
</tr>
<tr>
<td>Raspberry flavor</td>
<td></td>
</tr>
<tr>
<td>Final volume</td>
<td></td>
</tr>
</tbody>
</table>

Each formula was prepared as follows: Loratadine, methyl paraben, propyl paraben were levigated in a mortar with glycerol and the prepared dispersion of suspending agent. The mixture was triturated with a pestle until a smooth paste was formed. With continuous triturations, the paste was diluted with the remaining amount of the dispersion of the suspending agent then transferred to a graduated cylinder. Finally, the required amount of disodium EDTA and sorbitol were dissolved in a small portion of water, and added to the graduated cylinder and raspberry flavor was added and water to make the final volume. The suspension was shaken and the pH was adjusted to 5 with few drops of 5M sodium citrate.

In Vitro Evaluation of Suspension

Dissolution rate profile:

The dissolution rate of loratadine suspension was studied using USP dissolution apparatus type II which was provided with stainless steel stirrer connected to electric motor and rotated at 50 r.p.m. with 900 ml of 0.1N HCl placed in the dissolution jar and equilibrated at 37 °C. This was followed by transferring 5 ml of the prepared suspension to the jar bottom using a syringe. Then a sample of dissolution medium was withdrawn at different time intervals (2, 5, 15, 30, 45 and 60 minutes) through a pipette fitted with a filter paper. Fresh dissolution medium was added to the jar each time to replace withdrawn samples. Each sample was suitably diluted and assayed spectrophotometrically at 278 nm for loratadine content.

Measurement of rheograms:

Rheograms was obtained at 25 °C using Brookfield viscometer.

Sedimentation volume measurement

Fifty milliliters of each suspension was diluted with distilled water to a volume of 100 ml in a stopped graduated cylinder. The suspensions were shaken vigorously to insure uniformity, and then left undisturbed. The sedimentation volume was measured every 4 hours for period of 48 hours (17).

Resuspendability of suspension

The efforts required to convert the sedimented system to homogenous suspension upon shaking the cylinder manually, were rated with a ranks as follows: resuspendable, resuspendable with difficulty or not resuspendable (18).

Stability study

The accelerated stability study was done in order to determine the expiration date of the selected formula. The suspension was centrifuged to get the supernatant solution; 5ml samples of the resultant solution were stored in several closed amber glass containers at 35, 45 and 55 °C for 90 days. Samples were inspected for change in color, odor, pH, precipitant and assayed for drug content at suitable time intervals (0, 10, 20, 30, 45, 60 and 90) days.

Results and Discussion

Effect of type and concentration of suspending agent on the drug release:

The effect of various types of suspending agents (surfactants and polymers) on the dissolution rate of loratadine was investigated.

![Figure 1](image.png)

*Figure (1): Effect of polysorbate 40 concentration on the percent of loratadine released in 0.1 N HCl pH (1.2) at 37 °C.*
Figure (1) indicated that polysorbate 40 at all concentration used increases the amount of drug released in the following order: 0.0% < 0.5% < 2.0% 1.25% It was seen that increasing polysorbate 40 concentration from 0% to 0.5% and 1.25% (w/v) enhance the drug release, this may be attributed to the wettability and micellarization effect of polysorbate 40 at the interface between insoluble drug particles and the vehicle (19). Meanwhile increasing polysorbate 40 concentration to 2% (w/v) enhance the release of loratadine to a lesser extent compared with 1.25% (w/v), this odd behavior may referred mainly to the formation of micelle macromolecules of drug with polysorbate 40 that hinder the excessive drug release from insoluble loratadine particles, this behavior give an impression of critical micelle formation with this range of polysorbate 40 concentration (20).

From the other hand figures 2, 3 and 4 illustrate the effect of anionic hydrophilic polymers including xanthan gum, NaCMC and sodium alginate on the dissolution rate of loratadine using different concentrations of these polymers. The results indicated that the percent of drug release were as follows:

Xanthan gum 0.7% < 0.0% < 0.3% < 0.5%
NaCMC 0.0% < 1.0% < 0.25% < 0.5%
Sod. Alginate 2.0% < 1.0% < 0.5% < 0.0%

The hydrophilic polymers xanthan gum and NaCMC enhanced the dissolution rate of loratadine, since these polymers behave as protective colloid by coating the solid hydrophobic particles with multimolecular layer. This imparts hydrophilic character to the solid and thus promotes wetting (1), but to certain limits, then the dissolution rate of loratadine decreased by increasing xanthan gum and NaCMC above 0.5% (w/v), this result may be attributed to the increase in viscosity of the prepared formula (21, 22). Moreover the results showed that the presence of sodium alginate retarded the dissolution rate of loratadine at all concentrations used. This result is related to the formation of higher viscosity regions due to the hydrated polymer surrounding drug particles which encounter high resistance to the dissolution (23). On the other hand, the effect of veegum on the dissolution rate of loratadine is shown in figure(5). 0.0% < 2.0% < 1.5% < 0.5%
This retardation in dissolution of loratadine as the concentration of veegum increases may be attributed to adsorption of loratadine on veegum or solid particle films formed around the drug particles (24).

**Formulation of the loratadine suspension:**

Xanthan gum was used as a suspending agent in concentration of 0.5% to prepare formula A. This concentration gave the best release as mentioned previously. It is an effective flocculating agent at relatively low concentration and has excellent suspending properties to suspend solid (25). The rheological stability of xanthan gum toward pH changes encountered during transit through the gastrointestinal tract in addition to large sedimentation volume presumably by polymer bridging phenomena providing reasons for its use (26). NaCMC was incorporating in formula B in concentration of 0.5% and enhanced the dissolution rate of loratadine, but its aqueous dispersion has low viscosity and produced sediment layer that was easily redispersed by shaking. Farther more, a combination of xanthan gum and NaCMC (formula C) resulted in too viscous suspension which has less flexibility when was pouring. Veegum was chosen in a concentration of 0.5% (formula D), since this concentration gave the best release but this suspension had low viscosity. The linear branched chain molecules of veegum form a gel-like network within the system and became adsorbed on to the surface of the dispersed particles, thus holding them in flocculated state (27). So formula E was prepared with 2% veegum to get higher viscosity. The non-ionic surfactant polysorbate 40 was incorporated as a wetting agent and to increase the dissolution rate of loratadine. This dispersion exhibit thixotropy band plasticity with high yield value. It remained in the flocculated state (i.e., no hard sediment or caking was formed) and poured easily. The following excipients were added to the prepared suspension; sorbitol and glycerol as a sweetening agent. They produce pleasant taste, less viscous suspension and are better than sucrose in producing structure in vehicle suspension (28). Disodium edetate was involved in the formulation to protect loratadine from deterioration (29). Raspberry flavor as flavoring agent, methyl paraben and propyl paraben were added as preservatives. The pH of the formula was adjusted to 5 using 5M sodium citrate.

**In vitro evaluation of suspension:**

**dissolution rate profile:**

Table (2) and figure (6) showed the dissolution rate profiles of the prepared loratadine suspensions. The data indicated that formula A had the highest dissolution rate constant as compared with the other formulas, since the rate constant of formula A was $24.3 \times 10^{-3}$ (mg$^{1/3}$/min) using Hixson-Crowell root equation, that expresses the dissolution rate of solid particle based on the cube root of the weight of the particles (30), this equation was as follows:

$$W_0^{1/3} - W^{1/3} = Kt$$

Since: $W_0$=the original mass of the drug particles

$W$ = the mass of drug dissolved

$K$ = the cube root dissolution rate constant

$T$ = the time required to dissolve (W) mass of drug particles

Table (2): The calculated dissolution rate constants of loratadine in the prepared formulas.

<table>
<thead>
<tr>
<th>Formula</th>
<th>$K \times 10^{-3}$ (mg$^{1/3}$/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula A</td>
<td>24.3</td>
</tr>
<tr>
<td>Formula B</td>
<td>15.0</td>
</tr>
<tr>
<td>Formula C</td>
<td>21.3</td>
</tr>
<tr>
<td>Formula D</td>
<td>21.2</td>
</tr>
<tr>
<td>Formula E</td>
<td>21.5</td>
</tr>
</tbody>
</table>

**Figure (6): Dissolution rate profile of loratadine in the prepared formulas in 0.1N HCl at 37°C.**
Measurement of rheograms:

The rheograms of the prepared formulas are represented in figure (7). The profile showed that the viscosities of loratadine suspensions were shear rate dependent and it increased in the following order:

Formula C > D > A > B > E

The results also illustrated that all the prepared formulas exhibited pseudoplastic flow which evidenced by shear thinning and increase in shear stress with increased angular velocity. This behavior due to the suspending agent used, because as a general rule, the pseudoplastic flow is exhibited by polymer in solution[31]. The rheological properties of the prepared formulas revealed that formula A was the best one which offered ease of pouring and swallowing compared with formula B and E which they are less viscous and could not obtain the structured suspension with them. On the other hand, higher viscosity was obtained with formula C and D with a difficulty in the pouring and swallowing from the bottle orifice. This was a result of using a combination of two polymers (xanthan gum + NaCMC) and (xanthan gum + veegum) respectively which leads to rheological synergism to be occurred due to stronger cross-linking between the two polymers used, where the presence of carboxyl groups on NaCMC and xanthan gum promote stronger hydrogen bonding between them[32].

Sedimentation volume and resuspendability:

The sedimentation volume (F) is the ratio of the ultimate height of the sediment as suspension settles in a cylinder (Hμ) to the initial height of total suspension (H₀).

\[ F = \frac{H_\mu}{H_0} \]

While the Resuspendability is a quantitative test to evaluate the ease of redispersion of a suspension after a long period of standing[30].

Table (3) shows the sedimentation volume and Resuspendability of the prepared formulas.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Sedimentation volume F = H_μ / H_0</th>
<th>Resuspendability</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>No sedimentation</td>
</tr>
<tr>
<td>B</td>
<td>0.6</td>
<td>Easily resuspended</td>
</tr>
<tr>
<td>C</td>
<td>1</td>
<td>No sedimentation</td>
</tr>
<tr>
<td>D</td>
<td>0.9</td>
<td>Easily resuspended</td>
</tr>
<tr>
<td>E</td>
<td>0.4</td>
<td>Resuspendable with difficulty</td>
</tr>
</tbody>
</table>

Table (3) shows the sedimentation volume and Resuspendability of the prepared formulas. The data indicated that the formulas prepared with xanthan gum (formula A, C and D) had sedimentation volume almost equal to 1 i.e., no sedimentation was occurred during the test period. The obtained results attributed to the network of flocs formed in the suspension which is so loose and fluffy that can extend through out the extra vehicle[31]. Xanthan gum is often used as flocculating agent to achieve non-sedimenting suspension of drugs with no need to other adjuvant[18]. However, formula B had a sedimentation volume equal to 0.6 and was easily resuspended by shaking. This low sedimentation volume may be due to the type of the suspending agent used, since NaCMC may form homogenous network in all concentrations used[23]. On the other hand, formula E, which showed sedimentation during the test period, had low sedimentation volume of 0.4 and was resuspendable with difficulty, so it is pharmaceutically unacceptable.

Stability study:

Formula A was chosen for the stability study as the promising formula since it gave the optimum physical stability and remarkable release profile. The stability study carried at moderate exaggerated temperatures (35, 45 and 55 °C) to predict the expiration date of the promised formula. The degradation of loratadine followed apparent zero-order kinetics, since the concentration in solution depends on the drug solubility. As loratadine decomposes in solution, more drug is released from the suspended particles so that the concentration remains constant[30]. The resultant solution from centrifuging formula (A) was with no reservoir of loratadine to replace that depleted so loratadine degradation
in them followed first-order expression as in equation (1):
\[ \frac{d[A]}{dt} = K[A] \quad \text{.........(1)} \]
in which A is the concentration of loratadine remaining undecomposed at time t, and K is the first-order rate constant. When the concentration [A] is rendered constant, as in case of a suspension, equation (2) is applied:
\[ K[A] = K_0 \quad \text{.........(2)} \]
where \( K_0 \) is the apparent zero-order rate constant, [A] is the solubility of loratadine at 25°C which is equal to 0.096 gm/100ml and K is the first-order rate constant at 25°C. The first-order rate constant for loratadine degradation in supernatant centrifuged solution of formula A was calculated from the slopes of straight lines which resulted from plotting log percent remaining of loratadine in the solution versus time at elevated temperatures (35, 45 and 55°C) as shown in figure (8) and listed in table (4).

Then by plotting the log of these rate constants versus the reciprocal of the absolute temperatures, the first-order rate constant obtained was equal to 0.0749 \times 10^{-3} (day^{-1}) as shown in figure (9).

\[ K_0 = K[A] \]
\[ K_0 = 0.0749 \times 10^{-3} \text{ day}^{-1}, 0.096 \text{gm/100ml} \]
\[ K_0 = 0.71 \times 10^{-5} \text{gm/100ml day}^{-1} \]

Figure (8): Accelerated stability study of loratadine in the prepared suspension (formula A) at elevated temperatures.

Figure (9): Arrhenius plot for shelf life estimation of loratadine in the prepared suspension (formula A).

Then the expiration date of loratadine suspension (formula A) was calculated as follows: \[ t_{10\%} = 0.1[A]_o / K_0 \]
The expiration date was found to be equal to 3.8 years. The formula show good physical stability, as there was no discoloration, precipitation or any other physical changes after the storage period. The pH of the formula was 5.0 for whole the period.

Conclusions
A stable suspension of loratadine could be prepared and used efficiently using xanthan gum as a suspending agent (Formula A), since it provided an easily pourable suspension with no sedimentation with expiration date of 3.8 years.

References
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