FORMULATION AND EVALUATION OF LIDOCAINE HYDROCHLORIDE CHEWABLE TABLET

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ABSTRACT

Objective: The objective of this study was to formulate and optimize a chewable formulation of lidocaine hydrochloride using a 3² factorial design for optimized the superdisintegrant concentration.

Methods: Various concentrations of sodium starch glycolate (SSG) (13.33 mg, 26.66 mg, and 40 mg) of superdisintegrant and starch (50 mg, 83 mg, and 116.66 mg) were added in the formulation; nine formulations were prepared according to 3² factorial designs and evaluated. The responses were analyzed for analysis of variance using Design-Expert version 10 software. Statistical models were generated for each response parameter. The models were tested for significance. Procedure to manufacture chewable tablets by direct compression was established.

Results: The results show that the presence of a superdisintegrant is desirable for chewable formulation. The best-optimized batch F7 found the batch having starch of amount 11.66 mg and SSG 13.33 mg. All the prepared batches of tablets were within the range. Optimized batch F7 showed drug content 102.46±0.0543, wetting time 18±1.7320, friability 0.65±0.0216, and drug release rate 99.97±0.0124% at the end of 30 min.

Conclusion: It can be concluded that 3² full factorial design and statistical models can be successfully used to optimize the formulations, and it was concluded that the trial batch F7 is the optimized formulation which complies official specifications of chewable tablets. The optimized batch was evaluated for thickness, weight variation, hardness, friability, drug dissolution, and stability study for 3 months. The similarity factor was calculated for comparison of dissolution profile before and after stability studies. After 30 min the drug release rate for batch F7 was 90.97% (Table 6). Hence, the results of stability studies reveal that the developed formulation has good stability.

Keywords: Lidocaine hydrochloride, Chewable tablet, Sodium starch glycolate.

INTRODUCTION

Chewable tablets are designed for use by the children and such person who may have difficulty in swallowing the tablets. In addition, chewable tablets facilitate more rapid release and have more rapid absorption of the active ingredients, provide quick onset of action. Hence, it was decided to formulate robust, effective, and compliant chewable dosage form of lidocaine hydrochloride (HCl) for providing painless dentistry without needle, potentially decreasing the number of dental phobic patients. Dental disorders are usually associated with inflammation and moderate-to-severe pain. Lidocaine, amide derivative, is a safe anesthetic agent possesses a mild local anesthetic effect. Thus, it was attempted to design chewable tablet containing lidocaine HCl, mainly for the treatment of dentistry and enhanced patient compliance of paramount importance.

EXPERIMENTAL

Materials
Lidocaine hydrochloride provided by Aurobindo Pharma, Hyderabad and other ingredients included Lactose monohydrate, starch, sodium starch glycolate, mannitol, aspartame, mint flavor, talc, aerosil.

Methods
Formulation design [11,13]
Formulation development by direct compression method All the ingredients were separately weighed and shifted using mesh no 40. Lidocaine, lactose monohydrate, starch, SSG, and mannitol were passed through mesh no 30 aspartame and mint flavor were passed through 100 mesh and required quantities were blended for 10 min. Finally, the above blend was lubricated with magnesium stearate, talc, and aerosil for 2 min. The powder blend was evaluated for the flow properties and was found to be good. The evaluated blend was compressed into tablets of 563 mg weight each. Minimum of 50 tablets was prepared for each batch. The manufacturing formulas for the tablets used in the above method are given in Table 2.

Optimization of process variables
It is desirable to develop an acceptable pharmaceutical in the shortest period of time using minimum workforce and raw materials. In addition to the art formulation, full factorial design is an efficient method of indicating the relative significance of a number of variables and their interaction. Batches were made with the aid of factorial design. In the present study, effect of two variables was considered. Two variables were considered at three levels lower level (1), middle level (0), and upper level (+1); hence, it was 3² factorial design. Shown in table 1.

Based on initial trials, levels of starch were selected as 50, 83, and 116.66 mg, whereas SSG levels were 13.33, 26.66, and 40 mg, nine formulations were prepared according to 3² factorial designs and evaluated. The responses were analyzed for analysis of variance (ANOVA) using Design-Expert version 10 software. Statistical models were generated for each response parameter. The models were tested for significance.

Evaluation of granules
Untapped bulk density [1]
About 10 g powder was placed into 100 ml measuring cylinder. Volume occupied by the powder weight is noted without disturbing the cylinder and bulk density is calculated by the following equation;

Untapped bulk density = Mass of bulk drug/Volume of bulk drug [8]
Table 1: Summarizes the independent and dependent variables along with their coded and actual levels

| Factors (independent variables) | Levels used        | Response dependent variable |
|--------------------------------|--------------------|-----------------------------|
| A: Concentration of Starch     | -1: 50 mg          | % Cumulative drug release   |
| B: Concentration sodium starch glycolate | 0: 13.33 mg | 1: 116.66 mg |
|                                |                    |                             |

Table 2: Composition of chewable tablets as per 3² factorial design to achieve maximum % drug release within 30 min

| Ingredients                  | F1 (mg) | F2 (mg) | F3 (mg) | F4 (mg) | F5 (mg) | F6 (mg) | F7 (mg) | F8 (mg) | F9 (mg) |
|------------------------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Lidocaine                    | 200     | 200     | 200     | 200     | 200     | 200     | 200     | 200     | 200     |
| Lactose monohydrate          | 1.633   | 1.50    | 1.366   | 1.30    | 1.166   | 1.033   | 1.166   | 1.166   | 1.166   |
| Starch                       | 50      | 50      | 50      | 83      | 83      | 83      | 116.66  | 116.66  | 116.66  |
| Sodium starch glycolate      | 1.333   | 26.66   | 40      | 13.33   | 26.66   | 40      | 13.33   | 26.66   | 40      |
| Mannitol                     | 100     | 100     | 100     | 100     | 100     | 100     | 100     | 100     | 100     |
| Aspartame                    | 10      | 10      | 10      | 10      | 10      | 10      | 10      | 10      | 10      |
| Mint flavor                  | 0.5     | 0.5     | 0.5     | 0.5     | 0.5     | 0.5     | 0.5     | 0.5     | 0.5     |
| Talc                         | 6       | 6       | 6       | 6       | 6       | 6       | 6       | 6       | 6       |
| Aerosil                      | 12      | 12      | 12      | 12      | 12      | 12      | 12      | 12      | 12      |
| Total weight                 | 563     | 563     | 563     | 563     | 563     | 563     | 563     | 563     | 563     |

Tapped bulk density [4]

About 10 g powder was placed into 100 ml measuring cylinder. The cylinder is then subject to a fixed number of taps (~100 times) until the powder bed volume goes to the minimum level. Record the final volume and calculate the tap density by following equation:

\[
\text{Tapped bulk density} = \frac{\text{Mass of bulk drug}}{\text{Volume of bulk drug on tapping}}
\]

Compressibility index [8]

It is an important measure obtained from bulk density and is defined as:

\[
C = \frac{\text{Density of powder}}{\text{Tapped density}}
\]

Where, \(pb\) = Tapped density of powder

\(b\) = Bulked density of powder

If the particle bed is more compressible, the blend will be less flowable and flowing materials.

Hausner’s ratio [8]

Hausner’s of the drug is found out using the following formula:

\[
\text{Hausner’s ratio} = \frac{\text{Tapped bulk density}}{\text{Bulked density}}
\]

Angle of repose [8]

The frictional force of a powder can be measured by the angle of repose. It is defined as the maximum angle possible between the pile’s surface of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the friction of the particles producing a surface angle, which is in equilibrium with the force of gravitation.

The angle of repose was determined by the funnel method suggested by Newman. Angle of repose is determined by the formula:

\[
\tan \theta = \frac{h}{r}
\]

Where,

\(\theta\) = Angle of repose

\(h\) = Height of the cone

\(r\) = Radius of the cone base

Angle of repose < 30° shows the free flowing of the material.

Evaluation of chewable tablet

General appearance

The general appearance of a tablet is its visual identity and overall “elegance” is essential for consumer acceptance. General appearance includes tablet’s size, shape, color, presence or absence of any odor, taste, surface texture, physical flaws and consistency, and legibility of any identifying marking [2].

Size and shape

The size and shape of the tablet could be dimensionally described, monitored, and controlled [2].

Hardness

The hardness of the tablet from each formulation was determined using Monsanto type hardness tester. A significant strength of chewable tablet is difficult to achieve due to the specialized processes and ingredients used in the manufacturing. The limit of hardness for the chewable tablet is usually kept in a lower range to facilitate rapid disintegration in the mouth [7].

Weight variation [6]

A total of 20 tablets were selected randomly from the lot and weigh individually to check for weight variation. Weight variation specification as per I.P. is shown as follows:

Table thickness

Thickness was calculated using digital Vernier calipers. 10 tablets were taken and thickness was measured by micrometer [6].

Friability [7]

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability. A preweighed tablet was placed in the friabilator. Friabilator consists of a plastic chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each single revolution. The tablets were rotated in the friabilator for at least 4 minutes. At the end of test, tablets were dusted and reweighed; the loss in the weight of tablet is the measure of friability and is expressed in percentage as:

\[
\% \text{ friability} = \frac{(\text{loss in weight})}{(\text{initial weight})} \times 100
\]

Dissolution test [10]

In vitro dissolution studies for all the fabricated tablets were carried out using USP Type II apparatus at 50 rpm in 500 ml of phosphate buffer.
Table 3: Pre-compression evaluation parameters of lidocaine HCl tablets

| Formulation | Angle of repose (mm) | Loose bulk density (g/cc) | Tapped bulk density (g/cc) | Percent compressibility | Hausner’s ratio |
|-------------|----------------------|---------------------------|---------------------------|------------------------|-----------------|
| F1          | 36.52±0.0081         | 0.467±0.0418              | 0.706±0.0081              | 33.283±5.2910          | 1.498±0.0118    |
| F2          | 33.69±0.0235         | 0.5000±0.0216             | 0.665±0.0104              | 25.256±1.7450          | 1.320±0.0637    |
| F3          | 36.52±0.0056         | 0.5033±0.0169             | 0.769±0.0052              | 34.983±2.2578          | 1.538±0.0053    |
| F4          | 35.53±0.0509         | 0.477±0.0088              | 0.714±0.0016              | 33.133±1.6456          | 1.495±0.0294    |
| F5          | 33.69±0.0374         | 0.454±0.0154              | 0.714±0.0008              | 25.973±0.2735          | 1.573±0.0531    |
| F6          | 33.69±0.0849         | 0.5003±0.0175             | 0.666±0.0020              | 25.020±1.7578          | 1.332±0.0531    |
| F7          | 33.69±0.0535         | 0.476±0.0122              | 0.714±0.0033              | 33.333±1.7228          | 1.501±0.0496    |
| F8          | 35.53±0.1203         | 0.5000±0.0138             | 0.668±0.0065              | 25.253±1.7078          | 1.326±0.0286    |
| F9          | 36.52±0.0432         | 0.526±0.0036              | 0.769±0.0044              | 31.570±1.1920          | 1.461±0.0216    |

HCl: Hydrochloride

Table 4: Post-compression evaluation parameters of lidocaine HCl chewable tablets

| Formulation | Appearance | Thickness (mm) | Hardness (kg/cm²) | Friability (%) | Diameter (mm) | Weight variation (mg) | Wetting time (s) | Drug content (%) |
|-------------|------------|----------------|------------------|----------------|---------------|----------------------|------------------|------------------|
| F1          | +++        | 5.04±0.0124    | 6.4±0.0816       | 0.72±0.0167    | 12.05±0.0124  | 49.3±1.6200          | 21±1.5166        | 99.8±0.7190     |
| F2          | +++        | 5.29±0.0163    | 6.3±0.0816       | 0.68±0.0124    | 12.05±0.0163  | 55.4±1.6329          | 22±1.7320        | 99.24±0.3766    |
| F3          | +++        | 5.17±0.0262    | 5.8±0.0816       | 0.69±0.0124    | 12.04±0.0124  | 50.1±1.7320          | 23±4.0824        | 98.40±0.3350    |
| F4          | +++        | 5.39±0.0294    | 5.9±0.0816       | 0.64±0.0124    | 12.06±0.0173  | 51.7±1.7320          | 19±2.5166        | 98.70±0.0821    |
| F5          | +++        | 5.37±0.0169    | 5.6±0.0816       | 0.66±0.0124    | 12.04±0.0270  | 54.2±1.2909          | 22±1.6162        | 96.52±0.7729    |
| F6          | +++        | 5.37±0.0205    | 5.7±0.0816       | 0.68±0.0169    | 12.04±0.0081  | 54.2±1.4949          | 24±4.0414        | 98.39±0.1729    |
| F7          | +++        | 5.32±0.0047    | 5.9±0.0816       | 0.65±0.0216    | 12.03±0.0205  | 50.6±2.7080          | 18±1.7320        | 102.46±0.0543   |
| F8          | +++        | 5.32±0.0081    | 4.2±0.1241       | 0.66±0.0216    | 12.03±0.0169  | 55.9±2.0876          | 20±1.2909        | 100.45±0.0336   |
| F9          | +++        | 5.32±0.0081    | 4.5±0.1241       | 0.66±0.0124    | 12.03±0.0124  | 55.6±1.6329          | 25±2.1602        | 96.25±0.6313    |

Means±SD, n=3. •: Poor, ++: Acceptable, +++: Good, HCl: Hydrochloride, SD: Standard deviation

Fig. 1: Drug release profile of formulation F1–F5

Fig. 2: Drug release profile of formulation F6–F9

pH 6.8, maintained at 37±0.5°C for 30 min. 5 ml aliquot was withdrawn at the 5 time intervals, filtered through Whatman filter paper and assayed spectrophotometrically at 263 nm using Veego VDA6 spectrophotometer. An “equal volume of phosphate buffer pH 6.8,” which was prewarmed at 37°C was replaced into the dissolution medium after each sampling to maintain the constant volume throughout the test [9].

RESULTS AND DISCUSSION

The formulations were evaluated for pre-compression parameters and the values were found to be within the prescribed limits for all formulations. The angle of repose indicates good flow property for all the formulations. The results were presented in Table 3. IR spectroscopic studies indicated that the drug is compatible with all the excipients. The IR spectrum of lidocaine HCl and lidocaine HCl formulation containing higher proportion of excipients was found to be similar fundamental peaks and patterns, thus confirming that no interaction of drug occurred with the components of the formulation. The general appearance of formulated tablets was examined. The formulated tablets were found to be of appropriate size and shape. The compressed tablets possessed uniform size and shape. The peak and patterns, thus confirming that no interaction of drug occurred with the components of the formulation. The results were presented in Table 4. The diameter of the tablets was found in the range of 12.03±0.0124 mm–12.06±0.0173 mm, and thickness was found in the range of 5.04±0.0124 mm–5.39±0.0294 mm. The hardness was found to be in the range of 4.2±0.1241 kg/cm²–6.4±0.0816 kg/cm². The percentage friability of all formulations was found in the range of 0.64±0.0124%–0.72±0.0167% and value <1% is an indication of tablet with good mechanical resistance. The weight of one tablet is 563 mg and the acceptable deviation was ± 5%. The weight of all tablets was found to be uniform and within the acceptable limit. The drug content of all the tablets was found in the range of 96.52±0.0169%–102.46±0.0543%, which was within the acceptable limits (Table 4).

A total of nine formulations were formulated from F1 to F9. For formulation F1, F4, and F7, the drug was mixed with lower amount of SSG, i.e., 13.3 mg and starch 50 mg, 83 mg, and 116.66 mg, respectively, showing 95.78±0.0294%, 99.44±0.0205%, and 99.97±0.0124% drug release in 30 min. In case of formulation F2, F5, and F8, the drug was mixed with SSG 26.66 mg and starch 50 mg, 83 mg, and 116.66 mg, respectively, showing 98.99±0.5170%, 100.45±0.3366%, and 102.46±0.0543% drug release in 30 min. In case of formulation F3, F6, and F9, the drug was mixed with SSG 50 mg and starch 50 mg, 83 mg, and 116.66 mg, respectively, showing 95.78±0.0294%, 99.44±0.0205%, and 99.97±0.0124% drug release in 30 min.
193

Table 5: Stability studies data of lidocaine HCl tablets

| Parameters        | After 1 month |
|-------------------|---------------|
| Thickness (mm)    | 5.31          |
| Hardness (kg/cm²) | 5.9           |
| Friability (%)    | 0.64          |
| Diameter (mm)     | 12.03         |
| Weight variation (mg) | 560  |
| Wetting time (s)  | 17            |
| Assay (%)         | 101.66        |

HCl: Hydrochloride

Table 6: Drug release profile of optimize F7 batch

| Time interval | After 0 min (%) | After 5 min (%) | After 10 min (%) | After 15 min (%) | After 20 min (%) | After 25 min (%) | After 30 min (%) |
|---------------|-----------------|-----------------|------------------|------------------|------------------|------------------|------------------|
| After 1 month | 0               | 16.20           | 34.80            | 50.69            | 74.70            | 98.60            | 98.97            |

Table 7: Analysis of variance table (Partial sum of squares - Type III)

| Source                        | Sum of square | df value | Mean square | F value | p value | p value P>F |
|-------------------------------|---------------|----------|-------------|---------|---------|-------------|
| Model                         | 323.08        | 3        | 107.69      | 17.15   | 0.0046  | Significant |
| A Starch                      | 8.71          | 1        | 8.71        | 1.39    | 0.2918  |             |
| B sodium starch glycolate     | 96.80         | 1        | 96.80       | 15.42   | 0.0111  |             |
| Residual                      | 217.56        | 1        | 217.56      | 34.65   | 0.0020  |             |
| Cor total                     | 31.40         | 5        | 6.28        |         |         |             |
| Total                         | 31.40         | 5        | 6.28        |         |         |             |

Table 8: Regression output of R1 for 3² full factorial design

| Parameters       | Value | Parameters       | Value |
|------------------|-------|------------------|-------|
| Std. dev.        | 2.51  | R²               | 0.9114|
| Mean             | 109.56| Adj-R²           | 0.8583|
| CV%              | 2.29  | Pred R²          | 0.6642|
| PRESS            | 119.02| Adeq precision   | 13.638|
| -2loglikelihood  | 36.79 | BIC              | 45.58 |

Assay (% drug content)
Transfer accurate measured quantity of tablet, equivalent to about 150 mg of lidocaine HCl to 125 ml of conical flask, and protects from atmospheric moisture with stopper fitted with a tube containing silica gel. Add 20 ml of glacial acetic acid and two drops of crystal violet. Titrate immediately with 0.1 N perchloric acid VS to a blue end point. Perform a blank determination and make necessary correction. Each ml of 0.1 N perchloric acid is equivalent to 23.43 mg of C₁₄H₂₂N₂O₅ (Figs. 1 and 2).

Stability studies [12,14]
Stability study of optimized formulation (F7) was conducted for 3 months. The dissolution, drug content of chewable tablets was tested each month, and the values of these evaluation parameters have been mentioned in Table 5. No significant change was found on comparing the values of evaluation parameter before and after the stability study. Thus, formulation was indicated to be stable.

ANOVA for response surface linear model
The model F value of 17.15 implies the model is significant, shown in table 7. There is only a 0.46% chance that an F value this large could occur due to noise. Values of "p>F" <0.0500 indicate that model terms are significant. In this case B, AB is significant model terms. Values >0.1000 indicate that the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve model.

The "Pred R²" of 0.6642 is in reasonable agreement with the "Adj R²" of 0.8583; i.e. the difference is <0.05.00 indicate that model terms are significant. In this case B, AB is significant model terms. Values >0.1000 indicate that the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve model.

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor, and the intercept is not at the center of the design space. Shown in Fig. 3.

Fig. 3: Response three-dimensional surface plot for percent drug release at 30 min

116.66 mg, respectively, showing 95.20 ±0.0374%, 94.30 ±0.0124%, and 99.19 ±0.0612%. In case of formulation F3, F6, and F9, the drug was mixed with higher amount of SSG, i.e. 40 mg and starch 50 mg, 83 mg, and 116.66 mg showing 91.44±0.0124%, 89.81±0.0124%, and 88.17±0.0124%, respectively. Formula F7 was optimized the batch that shows drug highest drug release 99.97±0.0124%.
From actual factor equation and counterplot of percentage drug release versus independent variable, it was concluded that as amount of SSG decreases percentage drug release is increases.

All the prepared batches of tablets were within the range. Using Monsanto hardner tester, the strength of the tablets was tested. All the tablets showed good hardness. Batch F8 had minimum hardness 4.2 while F1 had maximum hardness 6.4. The friability was carried out for all the batches of tablets. The friability was <0.2% for all the blends and was satisfactory. Assay value of all prepared batches of lidocaine HCl tablets was within the range of 95%-105% of stated amount of lidocaine HCl. From the data obtained, drug release rate at 30 min for batches F1, F2, F3, F4, F5, F6, F7, F8 and F9 was found 95.78±0.0294%, 95.20±0.0374%, 91.44±0.0124%, 99.44±0.0205%, 94.30±0.0124%, 89.81±0.0880%, 98.97 ±0.0124%, 99.19±0.0612%, 88.17±0.0124% respectively.

From all obtained results, it was found that trails F1, F2, F3, F4, F5, F6, F8, and F9 show slow drug release up to 30 min, but the trail F7 was the best one shows almost 100% drug release at the end of 30 min which formulated with 2.4% of SSG and 21% of starch having 102.46% drug content.

CONCLUSION
Chewable tablet could be successfully prepared by direct compression method using lactose monohydrate, starch, SSG, mannitol, aspartame, mint flavor, t alc, and aerosol whose response was excellent. In vivo release rate studies showed that the drug release for chewable tablet was maximum in formulation F7 is 99.97±0.0124% at the end of 30 min.

Finally, it can be concluded that 3² full factorial design and statistical models can be successfully used to optimize the formulations, and it was concluded that the trial batch F7 is the optimized formulation which complies official specifications of chewable tablets. The lidocaine HCl chewable tablet with formulation F7 concluded that the robust, effective, and reproducible formula with local anesthetic action and drug release.

AUTHOR’S CONTRIBUTION
Mr. Asish Dev conceived of the presented idea. I developed the theory and performed the computations. Asish Dev verified the analytical methods. Mr. Subhalakanta Dhal helped me to provide drug sample. All authors discussed the results and contributed to the final manuscript.

CONFLICTS OF INTEREST
The authors declare that they have no conflicts of interest.

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