FO RMULATION AND IN VITRO EVALUATION OF SALBUTAMOL SULPHATE AND THEOPHYLLINE EXTENDED-RELEASE TABLETS USING MODIFIED POLYMERS

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ABSTRACT

Objective: The main objective of this research work was to design, prepare and evaluate extended release (ER) tablets of anti-asthmatic drugs (salbutamol sulphate and theophylline) by direct compression method using diverse ratios of hydroxypropyl methylcellulose (HPMC K100M) and ethyl cellulose (EC) along with some other excipients.

Methods: Extended-release matrix tablets of salbutamol sulphate and theophylline were successfully fabricated by direct compression method and coded the formulations as F1 to F7 depending on the ratios of modified polymers. The core tablets composed of hydrophilic polymers of various ethyl cellulose (EC) along with some other excipients.

Results: Prepared formulations were subjected to various assessment parameters i.e. friability test, hardness test, drug content consistency and In vitro dissolution tests.

Conclusion: The results obtained in this research work clearly showed a promising potential of extended-release tablets containing a specific ratio of HPMC K100M and ethylcellulose as a release rate controlling polymers for effective treatment of asthma and chronic obstructive pulmonary diseases (COPD). The extended-release matrix tablets using hydrophilic polymers, such as HPMC K100M and ethylcellulose in different ratios.

Keywords: Salbutamol sulphate, Theophylline, HPMC K100M, Ethylcellulose and Extended-release tablets

INTRODUCTION

Tablets have been the most preferred oral dosage form for the patients suffering from chronic diseases like bronchial asthma, chronic bronchitis and chronic obstructive pulmonary diseases (COPD) because of low-cost therapy and ease of administration [1, 2]. The traditional tablets provide only a single and transient release of the drug. The pharmaceutical effect has only seen for the time duration in which the concentration of the drug remains within the therapeutic range that can be best achieved with ER tablets [3]. The significance of administering single-dose extended-release tablet that has discharged over an extended timeframe instead of multiple doses becomes the area of interest for the formulation designing scientists in the Pharmaceutical industry [4]. The oral prolonged discharge dose form has been prepared for those medications that are comfortably absorbed from the gastrointestinal tract (GIT), have a short half-life and eliminated quickly from the bloodstream [5].

The terms sustained action, sustained discharge, controlled discharge, timed release, prolonged action, depot, extended action and repository formulations have been used to represent the novel drug delivery system (NDDS) and formulated to get an extended therapeutic effect by continuously discharging drug over a prolonged time period after administration of a single dose [6]. There might be several other reasons also for the attractiveness of these dosage forms viz. provides enhanced bioavailability of medication, lessening in the recurrence of administration to extend the timeframe of effective blood levels, reduces the fluctuation of the peak-rough level and adverse effects and possibly enhances the particular distribution of the medication [7].

Salbutamol sulphate and theophylline drugs show the synergistic effect in terms of producing prolonged bronchodilatation for the treatment of reversible bronchospasm and COPD [8]. The short half-life of salbutamol sulphate and theophylline (4 to 6 hr) drugs increases the frequency of drug administration as an immediate release dosage form but makes them the best candidates for the design of extended-release tablets [9]. The present study aims to formulate, fabricate and evaluate the once-daily dose of extended-release matrix tablets using hydrophilic polymers, such as HPMC K100M and ethylcellulose in different ratios.

MATERIALS AND METHODS

Materials

The drugs salbutamol sulphate and theophylline were obtained as a gift sample from Elegant Drugs Pvt. Ltd., Karnatak and Koves India Ltd. Chennai. Polymers HPMC K100M and ethylcellulose were purchased from Evonik Degussa and Titan Biotech Ltd., Bhiwadi, Rajasthan. All used reagents and chemicals were procured from commercial stores and also of a good analytical grade.

Methodology

Establishment of the calibration data

In order to conduct the in vitro drug dissolution studies, the calibration tables containing data of pure drugs using different solvents viz. 0.1N HCl, phosphate buffer (pH 6.8) and distilled water were constructed. Calibration data has been used to find out the concentration of unknown sample taken from the dissolution media during dissolution studies at an equal interval of time. For this, 10 mg of salbutamol sulphate was accurately weighed and transferred into a 10 ml volumetric flask containing approximately 5 ml of 0.1 N HCl Flask was then gently shaken to dissolve its contents and volume was finally made up to 10 ml using the same solvent and was labeled as stock.
solution "A". 1 ml of this solution was pipetted out in another volumetric flask and volume was made up to 10 ml with 0.1N HCl in order to obtain the resulting solution of 100 µg/ml; it was then labeled as stock solution "B". Finally by using stock solution "B", solutions of various concentrations such as 2, 4, 6, 8, 10, 12 µg/ml were prepared. 0.1N HCl was taken as blank and absorbance of different dilutions were taken at 277 nm (nanometer) similarly, standard plots of pure salbutamol sulphate were also constructed at the same λmax using phosphate buffer and distilled water.

Similarly, the same procedure was followed for the drug theophylline to prepare the dilutions of different concentrations i.e. 2, 4, 6, 8, 10, 12 µg/ml with all three solvents (0.1 N HCl, phosphate buffer and distilled water). The absorbance of all dilutions for theophylline was taken at 271 nm λmax  [10, 11].

Table 1 and 2 enlisted the standard curve data of salbutamol sulphate and theophylline in 0.1N HCl phosphate buffer (pH 6.8) and distilled water respectively.

**Preparation of extended-release tablets**

ER tablets of salbutamol sulphate and theophylline (F1-F7) were fabricated by developing the formulae utilizing variable concentrations of two polymers viz. HPMC K100M and ethylcellulose as shown in table 3. The concentrations of salbutamol sulphate and theophylline were kept consistent for all groups of formulations.

Salbutamol sulphate, theophylline and various excipients were weighed precisely apart from magnesium stearate and talc, after that blended in a mortar with a pestle for 10-15 min. After the blending of medications with excipients, the required quantity of talc and magnesium stearate was included and additionally blending was done for 4-5 min. The gross weight of every tablet was kept at 250 mg [12, 13].

**Table 3: Formulations of ER tablets of salbutamol sulphate and theophylline**

| Ingredients (mg)               | Formulation code |
|-------------------------------|-----------------|
|                               | F1  | F2  | F3  | F4  | F5  | F6  | F7  |
| Salbutamol sulphate           | 4   | 4   | 4   | 4   | 4   | 4   | 4   |
| Theophylline                  | 40  | 50  | 60  | -   | -   | 40  | 50  |
| HPMC K100M                    | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Ethylcellulose                | -   | -   | 60  | 75  | 60  | 75  |
| Lactose                       | 100 | 90  | 80  | 80  | 65  | 40  | 15  |
| Magnesium stearate            | 2   | 2   | 2   | 2   | 2   | 2   | 2   |
| Talc                          | 4   | 4   | 4   | 4   | 4   | 4   | 4   |
| Total weight                  | 250 | 250 | 250 | 250 | 250 | 250 | 250 |

**Evaluation of extended-release tablets**

Prepared formulations (F1-F7) were assessed for different parameters like hardness, friability, content uniformity and in vitro dissolution test.

**Friability**

To assess the capability of the tablet to withstand wear and tear in packing, handling and transporting, friability test was done by Roche Friabilator. Pick randomly twenty tablets and weight (W) and were subjected to the joined impact of wearing down and shock by utilizing a plastic chamber (25 rpm) dropping the tablets at a separation of 6 inches with each revolution, operated for 100 revolutions. Each tablet was dusted and reweighed (W) after completion of 100 revolutions. The % friability was calculated using this formula [14].

\[
\text{Friability} \% = \frac{W_0 - W}{W_0} \times 100 \quad \text{eq 1}
\]

**Tablet hardness**

This represents the pressure which is required to crush the tablet. Monsanto hardness tester was used to determine the hardness of prepared tablets. The average hardness and standard deviation were determined and the hardness of 4 kg is considered to be least for a satisfactory tablet [15, 16].

**Uniformity of drug content**

Assay of ER tablets of salbutamol sulphate and theophylline was performed in distilled water to find out the number of drugs present in one tablet. For this 2 tablets were weighed and powdered in a glass mortar and 250 mg of the powder equivalent to 4 mg of salbutamol sulphate and 100 mg of theophylline was placed in two separate 100 ml volumetric flasks and dissolved in 100 ml water. The resulting solution was filtered and absorbance was recorded at λmax 277 nm for salbutamol sulphate and λmax 271 nm for theophylline using UV visible spectrophotometer. The concentration

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of medications in milligram per millilitre was calculated from standard calibration plots of drugs [17, 18].

**In vitro drug release studies**

In vitro release of salbutamol sulphate and theophylline from ER tablets was obtained separately by using USP type II (Paddle Type) dissolution apparatus in 900 ml of phosphate buffer of pH 6.8 at the constant temperature of 37 °±0.5 °C at 50 rpm. Aliquots (5 ml) of the solutions were taken out from the dissolution apparatus at various time intervals and replaced with fresh dissolution medium to maintain the sink condition. Samples were filtered and the absorbance of these solutions was observed by using a double beam ultra-violet spectrophotometer at 277 nm and 271 nm for salbutamol sulphate and theophylline respectively against fresh phosphate buffer solution as the blank [19, 20%].

**RESULTS AND DISCUSSION**

**RESULTS**

Observations of evaluation of various parameters are depicted in table 4, 5 and 6. Table 5 and table 6 represents the % cumulative drug release versus time profile of in vitro dissolution studies for both drugs (salbutamol sulphate and theophylline).

**Table 4: Evaluation of extended release matrix tablets**

| Code | Hardness (Kg/cm²) | Friability (%) | Weight (mg) | Drug content (%) | Thickness (mm) |
|------|-------------------|----------------|-------------|------------------|---------------|
|      | mean±SD           | mean±SD        | mean±SD     | mean±SD          | mean±SD       |
| F1   | 5.5±0.40          | 0.49±0.068     | 249.6±3.32  | 95.57±0.560      | 248.5±2.49    |
| F2   | 5.8±0.35          | 0.46±0.016     | 250.4±2.25  | 99.67±0.106      | 95.42±0.42    |
| F3   | 5.1±0.21          | 0.30±0.073     | 248.7±2.31  | 97.51±0.66       | 99.65±0.71    |
| F4   | 5.3±0.24          | 0.32±0.065     | 248.7±2.31  | 98.49±1.34       | 99.18±0.38    |
| F5   | 5.4±0.21          | 0.41±0.064     | 249.5±2.31  | 97.41±0.37       | 97.48±0.65    |
| F6   | 5.7±0.11          | 0.48±0.091     | 252.3±2.68  | 101.93±0.42      | 101.11±0.31   |
| F7   | 5.3±0.14          | 0.41±0.072     | 248.5±2.49  | 102.23±0.82      | 99.68±0.43    |

All values are mean±SD of three determinations

**Table 5: In vitro drug release profile of salbutamol sulphate**

| Time (h) | F1   | F2   | F3   | F4   | F5   | F6   | F7   |
|----------|------|------|------|------|------|------|------|
|          | mean±SD | mean±SD | mean±SD | mean±SD | mean±SD | mean±SD | mean±SD |
| 0        | 0     | 0    | 0    | 0    | 0    | 0    | 0    |
| 1        | 32.5±0.33 | 26.49±0.83 | 18.20±0.53 | 09.20±0.53 | 08.56±0.29 | 14.22±0.80 | 11.87±0.66 |
| 2        | 46.4±1.34 | 36.50±0.62 | 25.69±0.40 | 13.69±0.40 | 13.31±0.58 | 28.56±0.84 | 15.21±0.61 |
| 3        | 57.9±0.62 | 44.24±0.77 | 39.38±0.82 | 21.30±0.82 | 20.86±0.22 | 40.01±0.60 | 22.31±0.24 |
| 4        | 72.6±0.13 | 59.50±0.53 | 51.42±0.19 | 27.42±0.19 | 27.77±0.49 | 57.59±0.62 | 28.29±0.47 |
| 5        | 99.0±3.56 | 71.34±0.73 | 65.29±0.07 | 36.29±0.07 | 37.54±0.91 | 75.52±0.73 | 38.05±0.84 |
| 6        | 99.1±7.63 | 81.29±0.80 | 76.18±0.73 | 49.18±0.73 | 45.38±0.37 | 84.09±0.96 | 52.73±0.09 |
| 7        | 99.1±2.78 | 99.08±0.44 | 85.51±0.78 | 60.51±0.78 | 50.11±0.47 | 92.44±0.38 | 61.24±0.67 |
| 8        | 99.3±0.45 | 99.85±0.61 | 89.44±0.91 | 71.44±0.91 | 60.32±0.27 | 95.32±0.24 | 78.06±0.42 |
| 12       | 99.4±0.35 | 99.59±0.57 | 91.19±0.65 | 71.19±0.65 | 71.22±0.31 | 96.35±0.54 | 84.16±0.65 |
| 24       | 99.4±0.18 | 99.55±0.51 | 92.67±0.87 | 73.67±0.87 | 71.62±0.27 | 97.99±0.55 | 86.01±0.69 |

**Table 6: In vitro drug release profile of theophylline**

| Time (h) | F1   | F2   | F3   | F4   | F5   | F6   | F7   |
|----------|------|------|------|------|------|------|------|
|          | mean±SD | mean±SD | mean±SD | mean±SD | mean±SD | mean±SD | mean±SD |
| 0        | 0     | 0    | 0    | 0    | 0    | 0    | 0    |
| 1        | 28.06±0.39 | 21.80±0.22 | 17.66±0.61 | 09.11±0.53 | 07.55±0.63 | 12.49±0.78 | 10.16±0.18 |
| 2        | 43.73±0.63 | 32.08±0.21 | 23.05±0.47 | 14.62±0.73 | 13.09±0.77 | 27.03±0.22 | 14.19±0.45 |
| 3        | 54.67±0.45 | 39.11±0.42 | 37.66±0.29 | 23.32±0.54 | 19.36±0.32 | 39.66±0.03 | 20.42±0.62 |
| 4        | 68.91±0.32 | 57.38±0.76 | 48.01±0.35 | 27.33±0.61 | 27.56±0.35 | 55.04±0.18 | 26.17±0.11 |
| 5        | 96.55±0.43 | 69.65±0.08 | 64.97±0.46 | 35.79±0.23 | 35.45±0.21 | 73.15±0.36 | 37.72±0.86 |
| 6        | 98.84±0.56 | 73.07±0.37 | 74.38±0.75 | 45.63±0.72 | 45.76±0.55 | 81.36±0.82 | 52.36±0.28 |
| 7        | 98.34±0.67 | 96.48±0.62 | 82.86±0.44 | 49.69±0.57 | 51.88±0.56 | 90.47±0.42 | 59.15±0.10 |
| 8        | 98.11±0.31 | 97.64±0.55 | 86.48±0.39 | 58.66±0.11 | 59.44±0.34 | 94.19±0.39 | 73.04±0.62 |
| 12       | 98.12±0.81 | 97.36±0.58 | 89.66±0.21 | 69.02±0.26 | 68.21±0.36 | 94.68±0.43 | 80.73±0.51 |
| 24       | 98.36±0.44 | 97.63±0.70 | 89.54±0.11 | 77.19±0.27 | 75.48±0.39 | 94.36±0.12 | 81.33±0.14 |
DISCUSSION

Prepared formulations were subjected to various assessment parameters and the findings obtained were within the limits which are depicted in table 4. The hardness of all the tablets was within a range of 5.1±0.12 to 5.8±0.32 kg/cm². Weight loss of all tablets in friability test lay in a range of 0.30±0.096 to 0.49±0.057 %. The % drug content for various tablet formulations was in the range from 95.57±0.560 to 102.23±0.82 % for salbutamol sulphate and 95.88±0.36 % to 100.11±0.31 % for theophylline. The F-6 containing HPMC K100M and ethylcellulose (2:3 ratios) was selected as the optimum formulation on the basis of the results of in vitro dissolution tests. It is seen that at the end of 8 hr, 95.32±0.24% salbutamol sulphate and 94.19±0.39 % theophylline were released from the formulation.

CONCLUSION

The extended-release tablets of salbutamol sulphate and theophylline using specific ratio (2:3) of HPMC K100M and ethylcellulose can be successfully fabricated by direct compression method. Concentrations and ratios of used polymers i.e. HPMC K100M and ethylcellulose can affect the release of the drugs from the dosage form. Among the prepared batches of ER tablets based on performance with respect to friability, hardness, uniformity of drug content and in vitro % cumulative drug release studies, F6 delivers the best results. The formulation F6 discharge required loading dose concentration and maximum percentage cumulative drugs release over a period of 8 h which is 95.32±0.24% for salbutamol sulphate and 94.19±0.39% for theophylline.

It can be concluded from the observations that formulation F-6 has achieved the objectives of extended-release formulations i.e. patient convenience by reducing dosing frequency, reduction in toxicity, enhanced effectiveness of the drug by localization at the site of action and cost-effectiveness as an ER once daily dosage form.

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AUTHORS CONTRIBUTIONS

Experimental design, guidance, supervision and review work for the research was done by Dr Naveen Goyal, Principal (Director), Roorkee College of Pharmacy, Roorkee, Uttarakhand. Experimental work, interpretation of result and writing of this manuscript was done by Anil Kumar, Assistant Professor, Roorkee College of Pharmacy, Roorkee, Uttarakhand. Both authors read and approve the final manuscript.

CONFLICTS OF INTERESTS

All authors have none to declare

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