Development and Characterisation of Salbutamol Sulphate Hydrogel Beads by Using Emulsion Internal Ionotropic Gelation Technique

Bathula Bharathi 1,*, Botla Sirisha 1, V Uma Maheshwara rao 2, P Vijaya lakshmi 3, M Ajitha 4, M Vidyaltha 5

1 Department of Pharmaceutics, CMR College of Pharmacy, Medchal, Telangana, India
2 Department of Pharmacognosy, CMR College of Pharmacy, Medchal, Telangana, India
3 Department of Pharmaceutics, Gurunanak College of Pharmacy, Hyderabad, Telangana, India
4 Center for pharmaceutical sciences, IST, JNTH, Hyderabad, India
5 Karnataka College of pharmacy, Bangalore, India

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The purposes of this research was to development and characterize an oral, pulsatile, colon specific hydrogel beads to achieve time and/or site specific release of Salbutamol sulphate based on chronopharmaceutical approach. Emulsion internal ionotropic gelation has been suggested an alternative to as extrusion/external gelation in the encapsulation of several compounds including anti asthmatic drugs such as Salbutamol sulphate. Salbutamol sulphate is short acting beta-adrenergic agonists which are used only for symptomatic relief of asthma. Nocturnal asthma needs chronotherapeutic approach and Salbutamol sulphate has short half life with a bioavailability of 30-50% orally. In order to provide a oral colon specific action after predetermined lag time this was chosen as the model drug. Hydrogel beads containing Salbutamol sulphate were prepared by emulsion internal ionotropic gelation technique. Various polymers like sodium alginate and chitosan were used in different concentrations in the preparation of hydrogel beads. All the formulations were evaluated for surface morphology, particle size analysis, drug content, entrapment efficiency, swelling index, in vitro drug release was carried out in pH 1.2 buffer, pH 6.8 buffer and pH 7.4 buffer for 2 hours,3 hours and 3 hours respectively to mimic the conditions in GIT. It is concluded that hydrogel beads are the potential system for oral pulsatile colon specific delivery of Salbutamol sulphate for chronotherapy of nocturnal asthma.

Keywords: Colon specific, nocturnal asthma, Salbutamol sulphate

1. INTRODUCTION
Emulsion internal ionotropic gelation has been suggested as an alternative to extrusion/external gelation in the encapsulation of several compounds including anti-asthmatic drugs such as Salbutamol sulphate.

Salbutamol sulphate is a short acting beta-adrenergic agonist which is used only for symptomatic relief of asthma.\(^1\)\(^,\)\(^2\) Salbutamol is given as the sulphate form for its broncho dilating properties in the management of disorders with reversible airways obstruction such as in asthma and in certain obstructive pulmonary disease. Nocturnal asthma needs chronotherapeutic approach and Salbutamol sulphate has short half life with a bioavailability of 30-50% orally. In order to provide oral colon specific action after predetermined lag time this was chosen as the model drug.\(^3\) Traditionally drugs are released in an immediate or extended pattern. Disease like Asthma results in increased airway responsiveness & worsening of lung function. These symptoms typically occur between midnight & especially around 4am.\(^4\) These systems have a peculiar mechanism of delivering the drug rapidly and completely after a lag time i.e., a period of “no drug release.” Though most delivery systems are designed for constant drug release over a prolonged period of time, pulsatile delivery systems are characterized by a programmed drug release, as constant blood levels of a drug may not always be desirable. Pulsatile systems are designed in a manner that the drug is available at the site of action at the right time in the right amount.\(^5\) These systems are beneficial for drugs having high first-pass effect, drugs administered for diseases that follow chronopharmacological behavior, drugs having specific absorption site in GIT, targeting to colon and cases where night time dosing is required.\(^6\) One the other hand colon specific drug delivery systems (CDDS) have been developing as one of the site specific drug delivery systems. Along with many applications in local and systemic delivery of drugs the CDDS would also be advantageous when a delay in absorption is desirable from a therapeutic point of view as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythm, such as nocturnal asthma, angina and rheumatoid arthritis. It is a well established fact that average residence time of a formulation in stomach is 2 hours, and that in intestine is 3 hours.\(^7\)\(^,\)\(^8\) Thus, average lag time for a formulation to reach colon is taken as 5 hours. Since the objective of the study was to formulate a drug delivery system for treatment of nocturnal asthma, it was desired to have almost 100% drug release in colon within 3 hours after the system reaches colon. It was desirable to have drug release below 10% till 5 hours. Thus, essentiality of the study was to protect drug release till 5th hour and have near to 100% drug release by 8th hour. An attempt has been made to develop multiparticulate dosage form instead of single dosage form as there are potential advantages of multiparticulate system which include no risk of dose dumping, reduced risk of local irritation, less inter and intra subject variability and increased bioavailability.\(^9\)

2. MATERIALS AND METHODS

Salbutamol sulphate purchased from Alkem Private limited, Mumbai, India. Sodium alginate Chitosan were obtained from SD Fine-Chemicals Limited, Mumbai, India. All other ingredients, reagents and solvents were of analytical grade.

Design of the experiment:

Developing Salbutamol sulphate hydrogel beads with the following independent variables: stirring speed, drug polymer ratio and span 80% three levels of each independent variable were used for the above design.

Preparation of salbutamol sulphate hydrogel beads:\(^10\)\(^,\)\(^11\)

Different concentrations of polymer solutions were prepared by dissolving the specified amount of...
polymer in 30 ml of hot water, and then drug was dispersed in this polymer solution using magnetic stirrer for 10 min. A suspension of Caco$_3$ was dispersed in to drug polymers solution. After homogenization, the mixture was added into liquid paraffin oil containing different concentrations of span80 (emulsifying agent) and emulsified at 200 rpm. After emulsification liquid paraffin containing glacial acetic acid mixture was added to w/o emulsion and stirring was continued to permit calcium carbonate solubulization. A solution of Cacl$_2$ containing tween20 was added to the partition to recover the gelled beads from oily phase by decantation. Hydrogel beads were washed with Cacl$_2$ containing tween20 to remove residual oil. Hydrogel beads were removed from oily phase by using an acetate buffer at pH 4.5 and successively washed with this buffer until no more oil was detected by optical microscope observation. A sample of prepared beads for formulae is examined under optical microscope to detect the presence of oil droplets. Furthermore a sample of the prepared beads is pressed between two filter papers to detect the presence of any oily droplets and finally hydrogel beads were dried for 48 hrs at room temperature.

**Evaluation parameters**

The prepared hydrogel beads were evaluated for shape and surface characteristics, particle size, drug content, entrapment efficiency, swelling index, in-vitro dissolution studies and stability studies.

**a. Fourier Transform Infrared Spectroscopy (FTIR):**

The IR absorption spectra of the pure drug and with different excipients were taken in the range of 4000-450cm$^{-1}$ using KBr disc method, 1-2 mg of the substance to be examined was triturated with 300-400mg of finely powdered and dried potassium bromide. These quantities are usually sufficient to give a disc of 10-15mm diameter and pellet of suitable intensity by hydraulic press. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks due to presence of excipients.

**b. Scanning electron microscopy analysis (SEM):**

The shape and surface characteristics were determined by scanning electron microscopy 12 (model-JSM, 35CF, jeol, Japan) using gold sputter technique. The samples for SEM were prepared by lightly sprinkling the beads on a double adhesive tape, which stuck to an aluminum stub. The stubs were than coated with gold to a thickness of ~300Å using a sputter coater and viewed under the scanning electron microscope. A working distance of 20nm, a tilt of zero-degree and accelerating voltage of 15kv were the operating parameters. Photographs were taken within a range of 50-500 magnifications.

**c. Particle size analysis:**

The particle size of Hydrogel beads was determined using optical microscopy method. 13 Hydrogel beads were counted for particle size using a calibrated optical microscope. After drying at 37°C for 48 hours, the mean diameter of the dried beads was determined by a sieving method using USP standard sieves. Observations are recorded in Table 2. The study was performed in triplicate.

**d. Drug Content:**

To ensure the consistency of dosage units, each unit in a batch should have active substance content within a narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or a part of a dose of an active substance in each dosage form. Beads from each formulation were powdered. Equivalent weight of beads was weighed and dissolved in 5ml of water in 50ml standard flask. Shake them and make up with pH 7.4 phosphate buffer and then centrifuge it. From that take 5ml of solution in 50 ml standard flask make up with pH 7.4 phosphate buffer. Generally, the drug content in any formulation should
fall within the limit of 90 – 110%. Observations are recorded in Table 2. The study was performed in triplicate.

e. Encapsulation efficiency:

Encapsulation efficiency (EE) is the amount of added drug (in percent) that is encapsulated in the formulation of the beads. The EE of drug from hydrogel beads can be calculated in terms of the ratio of drug in the final formulation to the amount of added drug. An accurately weighed amount 5mg of drug equivalent beads of the formulation of beads was dispersed in 100 ml of pH 7.4 phosphate buffer. The sample was ultrasonicated for 3 consecutive periods of 5 minutes each, with a resting period of 5 minutes each. It was left to equilibrate for 24 hours at room temperature, and then centrifuged at 3000 rpm for 15 minutes. The concentration of Salbutamol sulphate in the decanted buffer and washing solutions was determined by measuring the absorbance at 276nm using a UV-Visible Spectrophotometer (Shimadzu, Japan). The determinations were made in triplicate.

f. Swelling studies:

Swelling ratio was studied by measuring the percentage water uptake by the beads. The hydrogel beads (100 mg) were placed in 100 ml pH 1.2 buffer for 2 hrs then in 100ml of pH 6.8 buffer for next 3hrs and 100ml of pH 7.4 buffer for the remaining time and allowed to swell up to a constant weight. The beads were removed at definite time intervals from their respective swelling media and weighed after drying the surface water using filter paper. Swelling percentage is calculated according to the following formula,

Swelling index = (S-T) / T×100

Where,
S = The weight of the hydrogel beads after swelling.
T = The initial weight of the hydrogel beads.

g. In vitro drug release for beads:

Dissolution is considered as one of the most important quality control tests performed on pharmaceutical dosage forms and is now developing into a tool for predicting bioavailability, and in some cases, replacing clinical studies to determine bioequivalence. In vitro release studies of prepared Hydrogel beads were carried out using USP Type I dissolution apparatus (basket) at 100 rpm. Dissolution was carried out for a total period of 8 hours using 0.1 N HCl (pH 1.2) for first 2 hours, phosphate buffer (pH 6.8) for the next 3hours and pH 7.4 for the remaining time maintained at a temperature of 37±1°C. At periodic time intervals, 5 ml of sample withdrawn were filtered through 0.45 membrane filter, and concentration of drug in each sample was analyzed by UV spectrophotometer at 276 nm and cumulative percent drug release was calculated. Five milliliters of fresh dissolution media was added each time to maintain the sink conditions. The drug release at different time intervals was analyzed by UV. The study was performed in triplicate.

h. Stability Studies:

Stability studies were carried out at accelerated condition (25˚ C ±2˚ C at 75% RH ±5%RH), (30˚ C ±2˚ C at 75% RH ±5%RH) and (40˚ C ±2˚ C at 75% RH ±5%RH) for the optimized formulation F6. The beads were stored at (25˚ C ±2˚ C at 75% RH ±5%RH), (30˚ C ±2˚ C at 75% RH ±5%RH) and (40˚ C ±2˚ C at 75% RH ±5%RH) for accelerated temperature in closed high density polyethylene bottles for 3 months. The samples were withdrawn after predetermined Period of 1 month, 2 month and 3 month. The samples were analyzed for its drug content and In-vitro drug released.

Drug release kinetics

Zero order model:

To study the zero order release kinetics the release rate data are fitted to the following equation

F=K₀t
Where,
F is the fraction of drug release
\( K_0 \) is the rate constant
T is the release time

**First order model:**
This model has also been used to describe absorption and/or elimination of drug, the release of the drug which followed first order kinetic can be expressed by the equation

\[
\log C = \log C_0 - \frac{kt}{2.303}
\]

Where,
Co is the initial concentration of drug
K is the first order rate constant
t = the time

**Higuchi release model:**
To study the higuchi release kinetics, the release rate data was fitted to the following equation

\[
F = KH_t^{1/2}
\]

Where,
F is the amount of the drug release
Kh is the release time
t is the release time

**Korsmeyer and peppas model:**
The release rate date were fitted to the following equation,

\[
\frac{M_t}{M_{\infty}} = KM_t^n
\]

Where,
\( M_t/M_{\infty} \) is the fraction of drug release
KM is the release constant t is the release time

3. RESULTS AND DISCUSSION

**Particle Size:**
The particle size values ranged from 577.52±29.5µm to 590.67±40.2 µm for all formulations. The particle size of formulations F1, F2, F3 and F4 containing chitosan : drug in the concentrations ranging from 1:1 to 1:2 was found to be 585±42.8µm, 579.9±40.01µm, 584.9±48.02µm and 580.6±33.9µm.

The particle size of formulations F5, F6, F7 and F8 containing sodium alginate : drug concentration ranging from 1:1 to 1:2 was found to be 577.52±29.5µm, 590.67±40.2µm, 588.71±34.08µm and 586.90±48.64µm respectively. With increase in the polymer concentrations an increase in the particle size of the beads was observed.

**Percent yield:**
The percentage (%) yield values ranged from 56±42.3 to 83 for all the formulations.

**FTIR studies:**
3460.68 cm\(^{-1}\), 3021.53 cm\(^{-1}\), and 1466.55 cm\(^{-1}\) corresponding to the presence of functional groups such as Tri-methyl group, secondary amine group, and phenol group. The FTIR of salbutamol sulphate + Sodium alginate formulation has shown intense bands at 3473.80 cm\(^{-1}\), 3022.45 cm\(^{-1}\), and 1438.90 cm\(^{-1}\) which indicates no change in the functional groups such as Tri-methyl group, secondary amine group, and phenol group and confirmed undisturbed structure of Salbutamol Sulphate, which indicates no drug-excipient interaction.

**Swelling index:**
The swelling Index was in the range of 3.18 to 17.39 at the end of 8 hours when kept in different buffer mediums. In pH 1.2 buffer slight swelling was observed among all formulations F1 to F8. High swelling was observed during 3 to 6 hours in the presence of pH 6.8 phosphate buffer and a constant increase in swelling was observed in pH 7.4 buffer as well for all the formulations. F5, F6, F7, and F8 formulations’ containing sodium alginate and combination of chitosan and sodium alginate along with the drug was found to have swelling index of 3.26, 3.60, 3.65 and 3.72 respectively. Swelling index of all formulations except formulations containing combination of chitosan and sodium alginate was found to be increasing with increase in concentration of
polymer. It was observed that as combination of chitosan and sodium alginate concentration increases there was a decrease in swelling index.

**Entrapment efficiency:**

The entrapment efficiency values ranged from 79.53±1.54 to 95.49±1.05 for all the formulations. The entrapment efficiency of formulations F1, F2, F3, and F4 containing Chitosan + drug was found to be 79.53±1.54, 82.23±1.84, 84.97±1.2 and 90.57±0.58 for 1:1, 1:2, 1:1 and 1:2 ratios respectively.

The entrapment efficiency of formulations F5, F6, F7 and F8 containing sodium alginate, combination of chitosan and sodium alginate and drug in the concentrations ranging from 1:1 to 1:2 was found to be 89.76±0.33, 95.49±1.05, 88.18±0.1, and 83.73±0.43 respectively. With increase in the polymer concentrations an increase in the entrapment efficiency of the beads was observed.

For selected formulation entrapment was found to be more in F6. So it is indicated only optimum concentration is suggestable. From the above result F6 (drug and combination of chitosan and sodium alginate) was selected as a optimized formulation.

**Drug Content:**

The drug content ranged from 99.99±0.50% to 96.71±0.33% for all the formulations. The drug content for all the formulations was found to be within the limits.

**Drug release studies:**

All the Eight formulations of hydrogel beads were subjected to dissolution studies. Dissolution was carried out in USP type I apparatus at 100 rpm in the volume of 900ml dissolution media of 0.1N HCL for initial 2 hours then in pH 6.8 phosphate buffer for next 3 hours and in pH 7.4 phosphate buffer for last 3 hours. In pH 1.2 phosphate buffer after 2 hours the drug release for F1, F2, F3 and F4 was 8.99±0.73, 9.21±0.41, 11.25±0.42, 7.48±0.08, respectively. F3 showed a burst release in the 3rd hour in pH 6.8 by releasing 78.59±0.10% of the drug. F4 showed a drug release of 87.53±0.12 by the end of 4th hour. F1 and F2 showed a release rate of 99.61±0.35 and 98.79±0.12 respectively by the end of 5 hours. The drug was released prior to the predetermined lag time (5 hours) in all the four formulations so further work was done by changing the polymer.

In pH 1.2 phosphate buffer after 2 hours the drug release for F5, F6, F7, and F8 formulations was 10.75±0.12, 7.21±0.38, 5.84±0.27, and 8.34±0.45% respectively. F5, F6, F7 showed 98.46±0.41, 10.3±0.31, 98.9±0.42% drug release by the end of first 5 hours of dissolution study. In formulations F5, F6, F7 and F8 the drug was released prior to the predetermined lag time. So further work was done by decreasing the concentration of the polymers. F6 showed a release rate of 99.6±0.35 by end of 8th hour of dissolution study. In the formulation F6 lag time was maintained and drug released after 5 hours. It was observed that a proper lag time of 5 hours was maintained for the sodium alginate and chitosan.

**Stability studies:**

The optimized formulation was stored in different conditions to check the stability. Drug content of the optimized formulation F6 initially was 99.6%. At 25°C/60%RH the values of drug content were found to be 99.55, 99.53 and 99.51 in the 1st, 2nd and 3rd months respectively. At 30°C/75%RH the values of drug content were found to be 99.54, 99.52, and 99.50 % in the 1st, 2nd and 3rd months respectively. At 40°C/75%RH the values of drug content were found to be 99.56, 99.55 and 99.54 in the 1st, 2nd and 3rd months respectively.

From the above result it can be concluded that there was no significant change in physical and chemical properties of the Hydrogel beads of formulation F-6 after 3 Months.
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**Formulation of hydrogel beads of salbutamol sulphate:**

<table>
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<tr>
<th>Formulations</th>
<th>Drug</th>
<th>Chitosan</th>
<th>Sodium CaCo3 Spa</th>
<th>Liquid Glacial Tweek CaCl3</th>
<th>Spec ion Code (gm)</th>
<th>n (gm)</th>
<th>m, n 80 paraffil acetic n, d</th>
<th>Alginat (gm)</th>
<th>mL n, oil</th>
<th>acid(m/20ml) (gm/rpm)</th>
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**Evaluation of hydrogel beads:**

**Determination of drug entrapments efficiency, drug loading, and yield, swelling ratio**

| Table 2: Evaluation of percentage yield, drug entrapment efficiency, drug content |

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<tr>
<th>FORMULATION CODE</th>
<th>% SWELL</th>
<th>% S W E L L E N T R A N T</th>
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<td>% S W E L L E N T R A N T</td>
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<td>RATIO</td>
<td>EFFICIENCY</td>
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<td>F3</td>
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<td>F8</td>
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**In vitro- dissolution profile:**

<p>| Table 3: Dissolution data of prepared hydrogel beads |</p>
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<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
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<td>1</td>
<td>8.99±0.9 21±0.41</td>
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**Stability studies:**

<p>| Table 4: Dissolution data for kinetic models |</p>
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<th>Tim</th>
<th>Log</th>
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<td>4.486047</td>
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Table 5: Results of stability studies of optimized formulation F-6

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<th>Formulation Code</th>
<th>Parameters</th>
<th>Initial</th>
<th>1st Month</th>
<th>2nd Month</th>
<th>3rd Month</th>
<th>Limits as per Specifications</th>
</tr>
</thead>
<tbody>
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<td>25°C/60%RH</td>
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<td></td>
<td>Not less than 85%</td>
</tr>
<tr>
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<td>30°C/75% RH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not less than 85%</td>
</tr>
<tr>
<td>F-6</td>
<td>40°C/75% RH</td>
<td></td>
<td></td>
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<td>Not less than 85%</td>
</tr>
<tr>
<td>F-6</td>
<td>25°C/60% RH</td>
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<td>30°C/75% RH</td>
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<td>Not less than 110%</td>
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<tr>
<td>F-6</td>
<td>40°C/75% RH</td>
<td></td>
<td></td>
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<td>Not less than 110%</td>
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</table>
FTIR studies:

Fig 1: FT-IR spectra of Salbutamol sulphate

Fig 2: FT-IR spectra of Optimized formulation

Scanning electron microscopy analysis (SEM):

Fig 3: Scanning electron microscopy analysis (SEM) for optimized formula

Dissolution profiles of Salbutamol sulphate hydrogel beads:

Kinetic models:

(a) Zero Order Kinetics:

Fig 5: Zero order plots for optimised formulation

(B) First Order Kinetics:

Fig 6: First order plot for optimised formulation

(c) Higuchi Models:

Fig 7: Higuchi plot for optimised formulation

(d) Korsmayer Peppas Equations:

Fig 8: Korsmayer Peppas plot for optimised formulation

(e) Hixon Crowell Erosion Equation:
4. CONCLUSION
The present investigation was carried out to develop and characterize an oral, colon specific multiparticulate device (hydrogel beads) to achieve time and/or site specific release of Salbutamol sulphate based on chronopharmaceutical approach. Results of release studies indicate that combination of chitosan and sodium alginate beads offer a high degree of protection from premature drug release in simulated upper GIT conditions. These beads deliver most of the drug load in the colon. Thus, spherical combination of chitosan and sodium alginate hydrogel beads are a potential system for colon delivery of Salbutamol sulphate for treatment of nocturnal asthma.

5. REFERENCES

