A COMPARATIVE STUDY OF VARIOUS MICROENCAPSULATION TECHNIQUES: EFFECT OF POLYMER VISCOITY ON MICROCAPSULE CHARACTERISTICS

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ABSTRACT

It is a comparative study of salbutamol sulphate-ethylcellulose microcapsules prepared by three different microencapsulation techniques i.e. coacervation thermal change, solvent evaporation and coacervation non-solvent addition by adjusting the ratio of salbutamol sulphate to ethylcellulose. 

In vitro release profiles of microcapsules were studied using USP XXIV dissolution apparatus-I in 450 ml double distilled water maintained at 37°C at 50 rpm. Scanning electron microscopic results indicated that all microcapsules were aggregated, whitish and irregular in shape with good entrapment efficiency (86.34 to 97.83), production yield (87.91±1.34 to 98.33±1.37) and flow properties. Initial burst effect was observed in the drug release behavior from all microcapsules. A slight increase in actual drug loading but profound increase in mean diameter of microcapsules was observed with the increase in the viscosity of ethylcellulose. UV and FTIR spectroscopy, x-ray diffractometry and thermal analysis verified the absence of any strong chemical interaction between drugs and polymer. The drug release from all the formulations followed anomalous diffusion mechanism and was best fit to Higuchi’s kinetic model. The results suggest coacervation thermal change as an appropriate approach to develop slow-release multi-unit oral dosage form of salbutamol sulphate suggesting at least twice administration in every 24 hours.

Keywords: Salbutamol sulphate; microencapsulation; ethylcellulose; coacervation; solvent evaporation; viscosity grade.

INTRODUCTION

The number of patients with chronic diseases is increasing day by day. This situation necessitates the development of drugs for a longer period and taking a lot of medicines simultaneously, which can lead to a decrease in patient compliance. This problem is serious for drugs with short biological half lives because they must be taken more frequently. One method to solve such problems is to develop a dosage form capable of releasing the drug gradually. In this regard, microencapsulation has been used as one of the tools to formulate controlled drug delivery systems (Yamuda et al., 2001). Microencapsulation is the application of a thin coating to individual core materials that have an arbitrary particle size range from 5-5000 µm (Lachman et al., 1986).

Salbutamol sulphate is a potent β-2 adrenoceptor stimulant which is used for the treatment of reversible airways obstruction. It is readily absorbed from the gastrointestinal tract when administered orally. Its biological half life is about 4 to 6 hours (Martindale, 2002).

Ethylcellulose (EC) is generally considered as a nontoxic, biocompatible and nonbiodegradable polymer. These characteristics are the reasons of its extensive selection for the development of oral dosage forms, especially sustained release formulations. This is the reason why EC is extensively used for the development of oral multi-unit dosage forms (i.e. microcapsules). EC coated microcapsules have also demonstrated their capability to absorb pressure and therefore save the coating from fracture during tablet manufacturing process. This process involves the conversion of multi-unit system into a single unit dosage form by compression. This single unit system disintegrates slowly into sub-units when exposed to dissolution process (Rowe et al., 2003).

Some authors microencapsulated salbutamol sulphate using various polymers with thermal change and solvent evaporation techniques and studied the dissolution profiles of designed microcapsules. But no one has elaborated whether salbutamol sulphate is chemically stable and intact or not after its microencapsulation into ethylcellulose. Thus the objective of present work was to encapsulate salbutamol sulphate (SS) into ethylcellulose (EC) microshells by different techniques i.e. coacervation thermal change (Yazan et al., 1995), solvent evaporation (Amperiadou and Georgarakis, 1995; Erden and Celebi, 1996) and coacervation non-solvent addition (present research) and analyze the designed microcapsules by applying various statistical, mathematical and analytical approaches.
MATERIALS AND METHODS

Materials
Salbutamol sulphate (SS, Unexo Laboratories), Ethyl cellulose (EC, 22 cp, Sigma, USA), Cyclohexane (Merck, Germany), n-hexane (Merck, Germany), Acetone (Merck, Germany), Light Mineral oil (BDH, England), Toluene (Merck, Germany), Polyisobutylene (M.W. 2.800, Acros Organics, USA), Petroleum ether (40-60 °C, BDH, England), Methanol (Merck, Germany). All other chemicals of analytical grade were purchased through commercial sources.

Preparation of microcapsules
Coacervation-thermal change (CTC)
A weighed amount of EC (22cp, 1g) was dissolved in cyclohexane (20ml) by heating to 80°C with vigorous stirring. In this solution, weighed amount of finely pulverized SS (1g/2g/3g) was dispersed. Vigorous stirring was continued through the process. Then the temperature was reduced to induce phase separation using an ice bath. The product obtained was washed twice with n-hexane (100ml) at room temperature, air-dried and passed through sieve no. 40 to separate individual microcapsules (Yazan, Demirel, and Guler, 1995). M1, M2 and M3 microencapsulated formulations were prepared with 1:1, 1:2 and 1:3 SS:EC ratios.

Solvent evaporation (SE)
EC (22cp, 1g) was dissolved in acetone (20ml) and SS (1g/2g/3g) was dispersed in this solution with stirring for 20 minutes. The dispersion was poured into light mineral oil (100ml) containing tween 80 (1.3%) and stirred for 5h at 1100 rpm at room temperature to remove acetone completely by evaporation. The light mineral oil was decanted and the collected microcapsules were washed twice with n-hexane (100ml) at room temperature. The microcapsules were separated by filtration and air dried for 12h (Amperiadou and Georgarakis, 1995). M7, M8 and M9 microencapsulated formulations were prepared with 1:1, 1:2 and 1:3 SS:EC ratios.

Coacervation-non solvent addition (CNSA)
Weighed EC (EC, 22cp, 1g) was dissolved in toluene containing polyisobutylene (6% w/w) in a closed beaker with magnetic stirring (Velp, Europe) at 500 rpm for 6h followed by dispersion of SS (1g/2g/3g) in it. After stirring the system for 15 min, phase separation was induced by adding petroleum benzin (non-solvent). The product was transferred to ice bath for the solidification of microparticles. The microparticles were treated with chilled petroleum benzin five times. The stirring was continued throughout the procedure. Eventually, microparticles were washed with n-hexane and dried in air for 2 hours followed by drying in oven (Memmert, Germany) at 50°C for 4 h. M4, M5 and M6 microencapsulated formulations were prepared with 1:1, 1:2 and 1:3 SS:EC ratios. M10 and M11 microencapsulated formulations were also prepared by this technique using two other viscosity grades of EC (10 cp and 46 cp) with 1:2 SS:EC ratios, respectively.

Physical study of microcapsules
The size and shape of prepared microparticles was determined by light and scanning electron microscope.

At the end of each microencapsulation process, microcapsules were weighed immediately (M1) and after drying to a constant weight (M2) (Sah, 1997).

Microcapsule solvation (%) = (M1 / M2) × 100

Bulk density was determined by following formula (Lachman et al., 1986):

Bulk Density = Sample weight / Sample volume

Tap density was measured by employing the conventional tapping method using 10 ml measuring cylinder and the number of tapings was reduced to 100 as it was sufficient to bring about a plateau condition. Taped density was calculated by following formula:

Tapped density = Weight of microcapsules / Volume of microcapsules after 100 tapings

Compressibility index was calculated by following formula;

Ci = [(Initial volume – Final volume) / Initial volume] × 100

Hausnner’s ratio, another index of flowability of microcapsules, is calculated by following formula;

Hausnner’s ratio = Volume before taping / Volume after taping

Angle of repose was measured by passing microcapsules through a funnel on the horizontal surface. The height (h) of the heap formed was measured and radius (r) of cone base was also determined. The angle of repose (θ) was calculated by following formula (Shariff et al., 2007):

θ = tan⁻¹ h / r

Where r is the radius and h is the height.

Assay of salbutamol sulphate
An accurately weighed quantity of microcapsules from each batch was dissolved in small amount of methanol (about 5 ml) to dissolve EC coat. To it, 15 ml of distilled water was added and the solution was heated to evaporate methanol. Then final volume was made to 25 ml with distilled water, filtered to remove insoluble EC and
diluted to make volume up to 450 ml with distilled water. This solution was then analyzed spectrophotometrically at 276 nm, against its standard solution exposed to the same conditions. Three determinations of the microcapsule salbutamol sulphate contents from the same batch were made (Sajeev et al., 2002). The drug loading (%) was calculated using the following equation:

\[
\text{Drug loading(\%) = } \frac{\text{Amount of drug found in microparticles}}{\text{Amount of drug used for microencapsulation}} \times 100
\]

The encapsulation efficiency (%) was determined by the following equation:

\[
\text{Encapsulation efficiency(\%) = } \frac{\text{Actual drug loading}}{\text{Theoretical drug loading}} \times 100
\]

The percentage production yield of the produced microcapsules was calculated for each batch by dividing the weight of microcapsules (M) by the total expected weight of drug and polymer (Mt):

\[
\text{Production yield(\%) = } \frac{M}{Mt} \times 100
\]

Each determination was performed in triplicate (Hascicek et al., 2003; Soppimath et al., 2001).

**In vitro dissolution studies**

The USP XXIV apparatus I (rotating basket, six replicates, pharma test, Germany) method was used for in vitro dissolution studies of microcapsules in 450 ml distilled water at 50 rpm. An accurately weighed quantity of microcapsules containing salbutamol sulphate equivalent to 8 mg salbutamol was placed in dissolution medium maintained at 37±1°C. Five ml of the sample was sucked and filtered through milli pore filters (Pharma test, Hainberg, Germany) at 0, 30, 60, 90, 120, 150 and 180 minutes with an automatic sample collector (Pharma Test, Germany). The dissolution media were replaced by five ml fresh distilled water to maintain a constant volume in the dissolution flask. The samples of salbutamol sulphate were analyzed directly at 276 nm using UV-Visible spectrophotometer (Shimadzu 1601, Japan) (USP, 2007).

**Model analysis and Statistics**

**Model dependent approaches**

The methods investigated to compare drug release profiles can be classified into two categories: model dependent approaches and model independent approaches. Five model-dependent approaches (Zero order, First order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas) were used to compare drug dissolution profiles and interpret drug release kinetics from all formulations with the help of equations 1-5.

Zero Order Model (Khatun et al., 2004):

\[
M_t = M_o + K_o t
\]

First Order Model (Khatun et al., 2004):

\[
\ln M_t = \ln M_o + K_1 t
\]

Higuchi Model (Higuchi, 1963):

\[
M_t = M_o + K_H t^{1/2}
\]

Hixson-Crowell Model (Hixson & Crowell, 1931):

\[
M_t^3 - M_o^3 = K_{HC} t
\]

Korsmeyer-Peppas Model (Korsmeyer et al., 1983):

\[
\frac{M_t}{M_o} = K_t^n
\]

In these equations, \(M_t\) is the cumulative amount of drug released at any specified time point and \(M_o\) is the initial amount of drug in the formulation. \(K_o, K_1, K_H, K_{HC}\) and \(K_t\) are rate constants for zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models respectively. In equation (5), \(M_t/M_o\) is the fraction of the drug release at time \(t\) and \(n\) is the release exponent that characterizes different release mechanisms. The \(n\)-value is calculated from the slope of Korsmeyer-Peppas plot.

**Model independent approaches**

While ANOVA based procedures and pair wise procedures are the model independent approaches which are also exercised in this research work. For this purpose, one way ANOVA plus Post-Hoc analysis (Duncan and Tukey) for significance at \(P < 0.05\) was conducted for whole release profiles using SPSS version 12.0 (Polli et al., 1996). Pair wise procedures include the difference factor \(f_1\) [Eq. (6)] and the similarity factor \(f_2\) [Eq. (7)]. According to the FDA guidance, values of \(f_1\) between zero and 15 and of \(f_2\) between 50 and 100 ensure sameness or equivalence of the two dissolution profiles. In both equations, \(R_t\) and \(T_t\) represent the dissolution measurements at \(P\) time points of the reference and test, respectively (Koester et al., 2004).

\[
f_1 = \left[ \sum_{i=1}^{P} \left| R_t - T_t \right| / \sum_{i=1}^{P} |R_i| \right] \times 100
\]

\[
f_2 = 50 \log \left\{ 1 + (1/P) \left( \sum_{i=1}^{P} (R_t - T_t)^2 \right)^{1/2} \right\} \times 100
\]

**UV and FTIR spectroscopy**

Drug-polymer interaction was studied by UV spectroscopy. For this purpose, UV spectra of the following solutions were recorded in the range of 200-400 nm using UV-Visible spectrophotometer (Shimadzu 1601, Japan): (i) Pure SS solution in distilled water, (ii) Pure EC solution and (iii) The solution prepared for the determination of drug entrapment efficiency of drug loaded microparticles (Das and Rao, 2007). SS, EC and microparticles were also evaluated using FTIR spectroscopy (MIDAC M2000, USA) by KBr disc method. FTIR spectrum of each sample was taken in the range of 500-4500 cm\(^{-1}\).
**Thermal analysis**

Thermal analysis [differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and differential thermometric analysis (DTA)] of microparticles and its individual components was conducted by using TA Instruments (USA). Accurately weighed samples were heated on alumina pan at a constant rate of 10°C/min under a nitrogen flow of 40 ml/min.

**X-ray diffractometry**

X-ray powder diffractometric analysis of microparticles and its individual components was carried out by using D8 Discover (Bruker, Germany) to find out any change in the crystallinity of drug during microencapsulation. The samples were scanned from 8° to 70° diffraction angle range under the following conditions: Cu-K$_\alpha$ radiation 1.5406 Å (source), 4°/min scan speed, scintillation detector, primary slit 1 mm, secondary slit 0.6 mm.

**Estimation of swelling and erosion of tabletted microparticles**

SS-EC tabletted microparticles were also evaluated for their swelling and erosion behavior to verify anomalous diffusion (Al-Taani and Tashkoush, 2003). Each tablet matrix was weighed before and after dissolution in above mentioned specific conditions for particular time and after drying at 40°C for 48 h to determine their erosion. Swelling (%) and erosion (%) was estimated by following formulas;

\[
\text{Swelling} \% = \frac{S}{R} \times 100
\]

\[
\text{Erosion} \% = \frac{(T - R)}{T} \times 100
\]

Where T is the initial weight of the matrix; S is the weight of the matrix after swelling; and R is the weight of the eroded matrix.

**Batch reproducibility and stability on storage**

Three batches of microcapsules with different drug polymer ratio were prepared and their dissolution rates and drug contents were evaluated under the same conditions as given above. A particular number of microcapsules from each batch were packed in air tight amber glass bottles and stored at 25°C and 40°C. The drug contents and the dissolution behavior of microcapsules were tested monthly for three months following the same procedure as previously described.

**RESULTS AND DISCUSSION**

**Physical characterization**

EC was used as a shell material due to its safety, stability, hydrophobicity and perfect film forming nature among lipophilic polymers (Rowe et al., 2003). The study was focused on the effect of EC viscosity grades, drug polymer ratios and the type of microencapsulation technique on drug contents and release profiles.
Table 1: Physical characteristics of microcapsules prepared by coacervation-thermal change, coacervation- non-solvent addition and o/o emulsion solvent evaporation technique

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Drug: Polymer ratio</th>
<th>Entrapment Efficiency (%)</th>
<th>Production yield (M±S.D) %</th>
<th>Size(Mean Diameter) (M±S.D) µm</th>
<th>Hydration Rate (%)</th>
<th>t60% (M±S.D) (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>1:1</td>
<td>95.23</td>
<td>94.38±0.95</td>
<td>79.84±09.58</td>
<td>157.95</td>
<td>0.34</td>
</tr>
<tr>
<td>M2</td>
<td>1:2</td>
<td>95.91</td>
<td>94.97±0.83</td>
<td>80.51±13.54</td>
<td>167.39</td>
<td>0.93</td>
</tr>
<tr>
<td>M3</td>
<td>1:3</td>
<td>97.07</td>
<td>95.37±1.02</td>
<td>82.97±10.18</td>
<td>169.65</td>
<td>2.16</td>
</tr>
<tr>
<td>M4,5,7,10</td>
<td>1:1</td>
<td>96.68</td>
<td>97.48±1.21</td>
<td>83.67±19.31</td>
<td>176.19</td>
<td>0.35</td>
</tr>
<tr>
<td>M6,8,9,11</td>
<td>1:2</td>
<td>96.98</td>
<td>98.19±1.20</td>
<td>70.04±27.15</td>
<td>155.12</td>
<td>0.94</td>
</tr>
<tr>
<td>M4,5,7,10</td>
<td>1:3</td>
<td>97.83</td>
<td>98.33±1.37</td>
<td>72.01±19.71</td>
<td>176.28</td>
<td>2.16</td>
</tr>
</tbody>
</table>

Table 2: Rheological properties of microcapsules

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Bulk density (g/ml)</th>
<th>Taped density (g/ml)</th>
<th>Compressibility index (%)</th>
<th>Hausner’s ratio</th>
<th>Angle of repose</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>0.21</td>
<td>0.23</td>
<td>11.0</td>
<td>1.16</td>
<td>21.87°</td>
</tr>
<tr>
<td>M2</td>
<td>0.26</td>
<td>0.31</td>
<td>12.87</td>
<td>1.09</td>
<td>23.94°</td>
</tr>
<tr>
<td>M3</td>
<td>0.30</td>
<td>0.33</td>
<td>10.39</td>
<td>1.29</td>
<td>27.45°</td>
</tr>
<tr>
<td>M4</td>
<td>0.29</td>
<td>0.29</td>
<td>13.15</td>
<td>1.03</td>
<td>28.68°</td>
</tr>
<tr>
<td>M5</td>
<td>0.24</td>
<td>0.26</td>
<td>13.62</td>
<td>1.17</td>
<td>25.13°</td>
</tr>
<tr>
<td>M6</td>
<td>0.18</td>
<td>0.21</td>
<td>10.08</td>
<td>1.46</td>
<td>29.65°</td>
</tr>
<tr>
<td>M7</td>
<td>0.23</td>
<td>0.34</td>
<td>09.12</td>
<td>1.90</td>
<td>22.08°</td>
</tr>
<tr>
<td>M8</td>
<td>0.19</td>
<td>0.39</td>
<td>12.82</td>
<td>1.13</td>
<td>19.71°</td>
</tr>
<tr>
<td>M9</td>
<td>0.23</td>
<td>0.19</td>
<td>11.35</td>
<td>1.24</td>
<td>26.58°</td>
</tr>
<tr>
<td>M10</td>
<td>0.29</td>
<td>0.30</td>
<td>13.76</td>
<td>1.25</td>
<td>29.27°</td>
</tr>
<tr>
<td>M11</td>
<td>0.31</td>
<td>0.28</td>
<td>13.87</td>
<td>1.31</td>
<td>31.33°</td>
</tr>
</tbody>
</table>

Table 1 depicts excellent percentage production yield with good encapsulation efficiencies for all the formulations. Out of the three methods, CNSA showed highest percentage production yield and encapsulation efficiency which can be justified on the basis of less solubility of SS in the solvent (toluene).

Rheological properties of all formulations are expressed in terms of bulk density, tapped density, compressibility index, Hausner’s ratio and angle of repose (table 2). It was observed that bulk density decreased with the increase in drug polymer ratio. Present results are in agreement with that reported by four investigators (Shariff et al., 2007) who also reported that bulk density increased when the polymer concentration was decreased. Compressibility index of all six formulations is below 15% indicating excellent flow properties. Hausner’s ratio, for all formulations, was below 1.29 again indicating free flow of all formulations of microcapsules and similarly angle of repose for all formulations are below 30° indicating once again free flowing nature of microcapsules.

Model analysis and statistics
Model independent approaches
The designed microcapsules were characterized for their release behavior in double distilled water and were evaluated by mathematical kinetic models, the difference and similarity factors and one way ANOVA plus Post-Hoc Test. EC is a non-water soluble polymer. Therefore the release of water soluble drugs is mainly driven by permeation of the drug through the hydrophobic polymer.
A comparative study of various microencapsulation techniques

membrane within water filled pores (Breghausen et al., 2002). Thus, the release of salbutamol sulphate from its microcapsules was influenced by the core to wall ratio as given graphically in fig. 2. The application of analysis of variance elaborated that the change in the method of microencapsulation affected the release of SS from its microcapsules (p>.05).

Fig. 2: The dissolution profiles of salbutamol sulphate microcapsules in distilled water showing the effect of different techniques of microencapsulation on its dissolution behavior.

Fig. 3: The dissolution profiles of salbutamol sulphate microcapsules in distilled water showing the effect of different viscosity grades of ethylcellulose (10 cp, 22 cp and 46 cp) on its dissolution behavior.

Comparison between $t_{50\%}$ showed that the release of salbutamol sulphate from its CNSA microcapsules was the most rapid followed by from that of CTC and SE respectively. CNSA involves slow solidification of microcapsules with comparatively less pores and fractures in the EC shells which allow slow penetration of dissolution medium. This is the reason of slow release of SS from its microcapsules as compared to from that of CTC and SE. The rapid solidification of CTC microcapsules causes increased fractures in EC shells followed by comparatively fast SS release. Whereas the $t_{50\%}$ of SE microcapsules lies intermediate to that of other two. According to Duncan test, the $t_{50\%}$ of all batches of the microcapsules of same drug-polymer ratio lied in the same homogenous group (CTC=CNSA=SE) (p>.05). According to difference factor ($f_1$) and similarity factor ($f_2$), the release profiles of all batches of microcapsules of same drug-polymer ratio prepared by different techniques are similar to each other as their $f_1 < 15.00$ and $f_2 > 50.00$ (p > 0.05). With a decreasing core to wall ratio, the velocity of the drug release decreases. It can be assumed that with decreasing core to wall ratios, the wall thickness of microcapsules increases which then slows down the diffusion of dissolution medium into the microcapsules. The number of surface pores decreased with increasing polymer concentration (p<0.05) (Sajeev et al., 2002; Breghausen et al., 2002). However, the results indicate that release behavior is arbitrarily affected by particle size of microcapsules in the present work.

The observed in vitro drug release profiles from salbutamol sulphate microparticles were biphasic: an initial rapid drug release phase (burst) was followed by the slow and prolonged phase. The burst effect may be beneficial because a high initial release produces an instant effect which can be subsequently maintained for a prolonged period by a slower but continuous release of drug. The rank order of drug-polymer ratios for percentage drug burst was as follows: 1:1>1:2>1:3, as visible from plots. The rapid initial phase of release was thought to occur mainly by dissolution and diffusion of drug entrapped close to or at the surface of microparticles. The second and slower release phase was thought to involve the diffusion of drug entrapped within the inner part of the polymer matrix by means of aqueous channels of a network of pores. It has been already reported that an initial burst effect in release profile was observed especially (a) when the drug solubility is high, (b) loading dose in the polymeric matrix is large and (c) lack of critical polymer concentration. Additionally when polymer concentration is low, the hydrated polymeric matrix would be highly porous leading to rapid diffusion of the drug from the polymeric matrix (Erden and Celebi, 1996; Singh and Robinson, 1990).

Model dependent approaches

To obtain appropriate information, the whole drug release datas were evaluated using different kinetic models i.e. zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models. The best fit of these models to the release profiles was investigated (table 3). Model with the highest co-efficient of determination was accepted as more appropriate model for the present dissolution data. The release patterns from all the formulations were best explained by Higuchi square root model due to the highest linearity, followed by zero order and first order. It confirms that SS release occurs by the diffusion through the pores and not through the swollen matrix. Korsmeyer-Peppas model further verified the mode of SS release from all microparticles that was anomalous diffusion (Non-Fickian i.e. a combination of the diffusion and erosion mechanisms). The application of Hixson-Crowell equation to the release data indicated a change in surface
area and diameter of the microcapsules with the progressive dissolution of the polymer as a function of time.

**Effect of viscosity grade on encapsulated SS**

SS microcapsules were prepared using three different viscosity grades of EC by coacervation-non solvent addition technique with no change in other experimental parameters. The effect of viscosity grades on SS release kinetics is shown in fig. 3. It is observed that higher the viscosity grade, slower was the SS release especially in the initial stage (\(p<0.05\)). Duncan test places the release profiles of 10 cp and 22 cp in the same group other than that of 46 cp. It shows that there is a significant difference in the release pattern of SS for the different viscosity grades of coating material. Comparison between \(t_{50\%}\) showed that the release of salbutamol sulphate from its M3 microcapsules was the most rapid followed by from that of M5 and M11 respectively. M10 microcapsules receive a thin polymer shell with comparatively more pores and fractures in the EC shells which allow rapid penetration of dissolution medium. This is the reason of rapid release of SS from its microcapsules as compared to from that of M3 and M11. The M11 microcapsules receive comparatively thick EC shells resulting comparatively slow SS release. Whereas the \(t_{50\%}\) of M5 microcapsules lies intermediate to that of other two. According to difference factor \((f_1)\) and similarity factor \((f_2)\), the release profiles of following pairs of microcapsule formulations are different from each other: M10 VS M11 and M5 VS M11 as their \(f_1 > 15.00\) and \(f_2 < 50.00\). While M10 VS M3 has \(f_1 < 15.00\) and \(f_2 > 50.00\) that indicates the mutual similarity of the compared release profiles but to a very less extent (Singh and Robinson, 1990; Uddin et al., 2001).

**UV and FTIR spectroscopy**

The UV spectra of the pure drug solution and the solution prepared for the determination of drug entrapment efficiency of the drug loaded microparticles were of the same kind. The \(\lambda_{max}\) of pure SS was observed at 276nm on the UV spectra of the solution prepared for the determination of drug entrapment efficiency of the SS

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**Table 3:** Release rate parameters \(\left[ y\text{-equation } (Y=aX + b),\text{ determination co-efficient } (R^2)\right]\) and release exponent (n) for release data after fitting of the whole release profiles of salbutamol sulphate from its respective microcapsules into different mathematical models

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Zero Order</th>
<th>First Order</th>
<th>Higuchi</th>
<th>Hixson-Crowell</th>
<th>Korsmeyer-peppa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Y-equation</td>
<td>R^2</td>
<td>Y-equation</td>
<td>R^2</td>
<td>Y-equation</td>
</tr>
<tr>
<td>M1</td>
<td>15.539x + 44.624</td>
<td>.424</td>
<td>-0.3843x + 3.7599</td>
<td>.547</td>
<td>39.993x + 24.177</td>
</tr>
<tr>
<td>M2</td>
<td>18.212x + 34.423</td>
<td>.615</td>
<td>-0.4584x + 4.1116</td>
<td>.808</td>
<td>43.092x + 14.961</td>
</tr>
<tr>
<td>M3</td>
<td>14.457x + 21.045</td>
<td>.713</td>
<td>-0.2251x + 4.377</td>
<td>.813</td>
<td>32.858x + 7.2019</td>
</tr>
<tr>
<td>M4</td>
<td>15.43x + 34.394</td>
<td>.434</td>
<td>-0.3702x + 3.8117</td>
<td>.560</td>
<td>39.505x + 23.335</td>
</tr>
<tr>
<td>M5</td>
<td>17.961x + 33.105</td>
<td>.626</td>
<td>-0.4312x + 4.1403</td>
<td>.807</td>
<td>42.31x + 14.133</td>
</tr>
<tr>
<td>M6</td>
<td>13.977x + 19.367</td>
<td>.727</td>
<td>-0.2251x + 4.377</td>
<td>.813</td>
<td>31.571x + 6.2169</td>
</tr>
<tr>
<td>M7</td>
<td>16.048x + 46.244</td>
<td>.423</td>
<td>-0.435x + 3.6912</td>
<td>.571</td>
<td>41.3x + 25.13</td>
</tr>
<tr>
<td>M8</td>
<td>18.589x + 37.536</td>
<td>.585</td>
<td>-0.5205x + 4.0314</td>
<td>.799</td>
<td>44.535x + 17.015</td>
</tr>
<tr>
<td>M9</td>
<td>14.881x + 23.667</td>
<td>.681</td>
<td>-0.2607x + 4.3095</td>
<td>.788</td>
<td>34.273x + 8.8797</td>
</tr>
<tr>
<td>M10</td>
<td>17.473x + 36.68</td>
<td>.571</td>
<td>-0.4376x + 4.0471</td>
<td>.764</td>
<td>42.102x + 17.103</td>
</tr>
<tr>
<td>M11</td>
<td>14.807x + 25.452</td>
<td>.650</td>
<td>-0.264x + 4.2766</td>
<td>.759</td>
<td>34.537x + 10.222</td>
</tr>
</tbody>
</table>
A comparative study of various microencapsulation techniques

loaded microparticles. Some characteristic and prominent peaks of SS were observed in FTIR spectrum. The spectrum of all microparticles showed amino, hydroxyl and aromatic stretchings at the same values as in that of pure SS which confirmed drug. No significant alteration in the nature of peaks denied any strong SS-EC interaction when SS was encapsulated into EC coats. The relevant FTIR spectras are given in fig. 4.

**Thermal analysis**
Thermal analysis showed good stability of SS in the form of all microparticles (fig. 5). The characteristic, well-recognizable thermal profile of the drug in a specific temperature range was observed. The same thermal behavior was observed in case of its all microparticles but with the loss of its sharp appearance that indicated a significant reduction of drug crystallinity in the polymer matrix. It indicated the absence of any strong chemical interaction between drug and polymer.

**X-ray diffractometry**
X-ray diffractometry revealed amorphous and crystalline nature of pure EC and SS respectively as shown in diffractograms (fig. 6). However, a decrease in the signal intensity i.e. crystallinity of SS was observed in microparticle form as compared to pure components.

**Estimation of swelling and erosion of tabletted microparticles**
The optimum formulations undergoes swelling and erosion continuously with time (h) after putting into dissolution apparatus as clear from fig. 7. This phenomenon is responsible for the gradual release of drug from tabletted microcapsule matrix. It also confirms anomalous diffusion of SS from tabletted microparticles.

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**Fig. 4: FTIR spectras**
CONCLUSION

In conclusion, there is no significant difference in terms of the physical properties of microcapsules prepared by these three techniques. However, this study elaborated that CTC is an appropriate method to microencapsulate salbutamol sulphate into the ethylcellulose shells because of its good entrapment efficiency, sustained drug release behavior, rapidness and ease. It could be concluded that the variation observed in entrapment efficiency,
production yield, mean particle size and the drug release behavior among the formulations are the result of the drug polymer ratio employed. These results may suggest the potential application of ethylcellulose microparticles as a suitable sustained release drug delivery system. Therefore, it is possible to formulate a single-unit, sustained-release oral dosage form of salbutamol sulphate at least twice in every 24 hours using ethylcellulose.

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REFERENCES


