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

GHULAM MURTAZA*, MAHMOOD AHAMD, NAVEED AKHTAR AND FATIMA RASOOL

Department of Pharmaceutics, Faculty of Pharmacy and Alternative Medicines, The Islamia University of Bahawalpur, Bahawalpur 63100, Pakistan

ABSTRACT

It is a comparative study of salbutamol sulpahte-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 sulpahte 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 sulpahte 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). Micro-encapsulation 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 micro-capsules 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 sulpahte (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.

**Corresponding author:* Tel: +92-62-9255243, Fax: +92-62-9255565, e-mail: gmdogar356@gmail.com

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). M_1, M_2 and M_3 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). M_7, M_8 and M_9 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 6 h 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. M_4, M_5 and M_6 microencapsulated formulations were prepared with 1:1, 1:2 and 1:3 SS:EC ratios. M_{10} and M_{11} 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 (M_1) and after drying to a constant weight (M_2) (Sah, 1997).

$$\text{Microcapsule solvation (\%)} = (M_1 / M_2) \times 100$$

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

$$\text{Bulk Density} = \text{Sample weight} / \text{Sample volume}$$

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 was calculated by following formula:

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

Compressibility index was calculated by following formula;

$$Ci = \{(\text{Initial volume} - \text{Final volume}) / \text{Initial volume}\} \times 100$$

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):

$$\theta = \tan^{-1} h / r$$

Where re 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 spctrophotometrically 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 (M_t):

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

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 sulpahte 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 sulpahte were analyzed directly at 276 nm using a 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):	$M_t = M_o + K_o t$	(1)
First Order Model (Khatun *et al.,* 2004):	$\ln M_t = \ln M_o + K_1 t$	(2)
Higuchi Model (Higuchi, 1963):	$M_t = M_o + K_H t_{1/2}$	(3)
Hixson-Crowell Model (Hixson & Crowell, 1931):	$M_o^3 - M_t^3 = K_{HC} t$	(4)
Korsmeyer-Peppas Model (Korsmeyer *et al.,* 1983):	$M_t/M_\alpha = K_k t^n$	(5)

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_k are rate constants for zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models respectively. In equation (5), M_t/M_α 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).

$$f_1 = \{[\sum_{i=1}^{P} |R_t - T_t|] / [\sum_{i=1}^{P} R_t]\} \quad (6)$$

$$f_2 = 50 \log \{[1 + (1/P)\sum_{i=1}^{P} (R_t - T_t)^2]^{-1/2} * 100\} \quad (7)$$

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_∞ radiation 1.5406 A° (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 Tashtoush, 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;

$$\text{Swelling (\%)} = S/R \times 100 \quad (8)$$

$$\text{Erosion (\%)} = (T - R)/T \times 100 \quad (9)$$

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.

SS containing microcapsules were prepared by various methods as mentioned earlier. Coacervation Thermal change was the most rapid of the three methods. The approximate time consumed for the preparation of microcapsules by SE, CTC and CNSA were 7 h, 10 h and 4 h, respectively.

The microcapsules were aggregated, whitish and irregular in shape (fig. 1). Table 1 shows the comparison of mean particle size of the microcapsules prepared by these three techniques. The smallest particle size was achieved by SE technique. Insignificantly larger size microparticles, prepared by other methods, may be due to the aggregation of individual microparticles which may also account for their slow release of SS due to slow penetration of dissolution medium into aggregated microcapsules (Sajeev *et al.,* 2002).

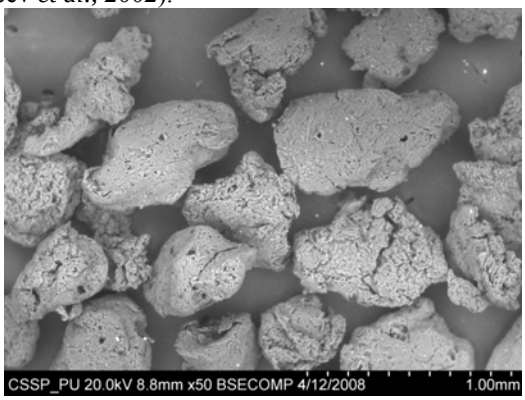

Fig. 1A: Scanning electron micrographs of M_2

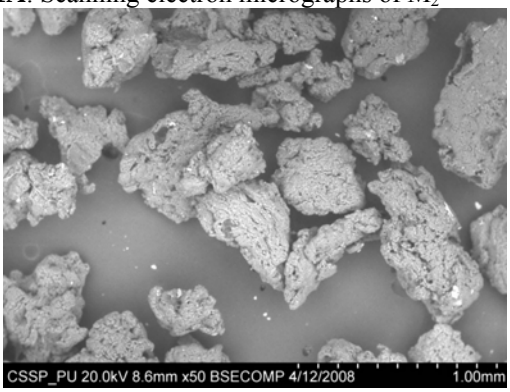

Fig. 1B: Scanning electron micrographs of M_5

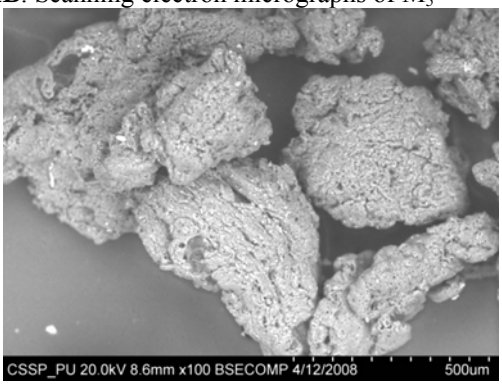

Fig. 1C: Scanning electron micrographs of M_8

Table 1: Physical characteristics of microcapsules prepared by coacervation-thermal change, coacervation- non-solvent addition and o/o emulsion solvent evaporation technique

Formu-lations	Drug: Polymer ratio	Entrapment Efficiency (%)	Production yield (M±S.D) %	Size(Mean Diameter) (M±S.D) μm	Hydration Rate (%)	$t_{60\%}$ (M±S.D) (hrs)
$M_1^{\dagger}$	1:1	95.23	94.38±0.95	79.84±09.58	157.95	0.34
$M_2^{\dagger}$	1:2	95.91	94.97±0.83	80.51±13.54	167.39	0.93
$M_3^{\dagger}$	1:3	97.07	95.37±1.02	82.97±10.18	169.65	2.16
$M_4^{\ddagger}$	1:1	96.68	97.48±1.21	68.37±19.31	176.19	0.35
$M_5^{\ddagger}$	1:2	96.98	98.19±1.20	70.04±27.15	155.12	0.94
$M_6^{\ddagger}$	1:3	97.83	98.33±1.37	72.01±19.71	176.28	2.16
M_7^{*}	1:1	86.34	87.91±1.34	43.57±18.28	183.64	0.23
M_8^{*}	1:2	89.84	89.27±1.19	45.98±11.54	181.65	0.86
M_9^{*}	1:3	92.78	88.93±1.13	48.04±21.07	169.52	2.01
$M_{10}^{\ddagger}$	1:2	97.06	98.17±1.40	70.91±18.45	159.87	1.19
$M_{11}^{\ddagger}$	1:2	97.23	98.51±1.13	71.12±32.11	163.27	1.72

Table 2: Rheological properties of microcapsules

Formulations	Bulk density (g/ml)	Taped density (g/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose
M_1	0.21	0.23	11.0	1.16	21.87°
M_2	0.26	0.31	12.87	1.09	23.94°
M_3	0.30	0.33	10.39	1.29	27.45°
M_4	0.29	0.29	13.15	1.03	28.68°
M_5	0.24	0.26	13.62	1.17	25.13°
M_6	0.18	0.21	10.08	1.46	29.65°
M_7	0.23	0.34	09.12	1.90	22.08°
M_8	0.19	0.39	12.82	1.13	19.71°
M_9	0.23	0.19	11.35	1.24	26.58°
M_{10}	0.29	0.30	13.76	1.25	29.27°
M_{11}	0.31	0.28	13.87	1.31	31.33°

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, taped 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

membrane within water filled pores (Breghausen *et al.,* 2002). Thus, the release of salbutamol sulpahte 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).

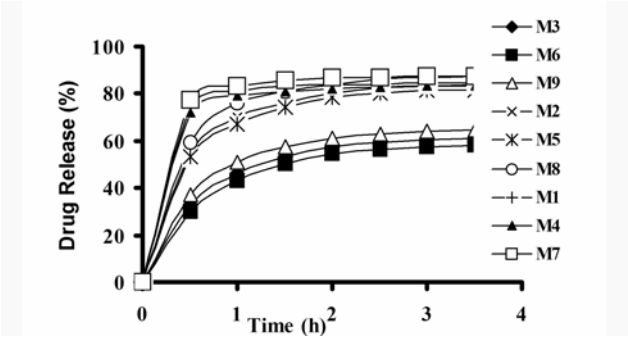

Fig. 2: The dissolution profiles of salbutamol sulphate microcapsules in distilled water showing the effect of different techniques of microencapsulation on its dissolution behavior.

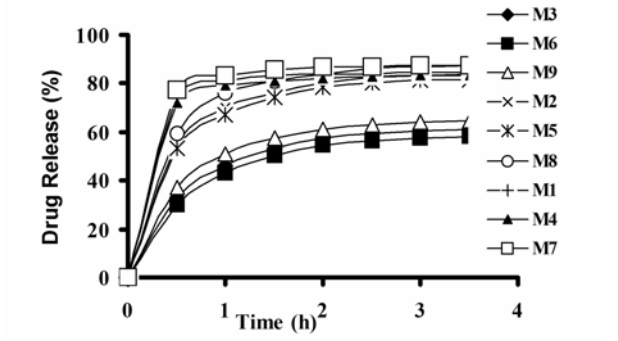

Fig. 3: The dissolution profiles of salbutamol sulphate microcapsules in distilled water showing the effect of different viscosity grades of ethylcellulose (10 cp, 22 cp and 46 cp) on its dissolution behavior.

Comparison between $t_{50\%}$ showed that the release of salbutamol sulpahte 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 sulpahte 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

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

Formul-ations	Zero Order		First Order		Higuchi		Hixson-Crowell		Korsmeyer-peppa		
	Y-equation	R^2	Y-equation	R^2	Y-equation	R^2	Y-equation	R^2	Y-equation	R^2	n
M_1	15.539x + 44.624	.424	-0.3843x + 3.7599	.547	39.993x + 24.177	.708	-0.4243x + 3.6043	.499	0.7211x + 3.5248	.093	.72
M_2	18.212x + 34.423	.615	-0.4584x + 4.1116	.808	43.092x + 14.961	.869	-0.5065x + 3.9621	.745	0.8431x + 3.3918	.132	.84
M_3	14.457x + 21.045	.713	-0.2251x + 4.377	.813	32.858x + 7.2019	.929	-0.2952x + 4.3068	.786	0.8933x + 2.9953	.179	.89
M_4	15.43x + 43.394	.434	-0.3702x + 3.8117	.560	39.505x + 23.335	.717	-0.4141x + 3.654	.511	0.7238x + 3.5059	.095	.72
M_5	17.961x + 33.105	.626	-0.4312x + 4.1403	.807	42.31x + 14.133	.876	-0.4857x + 3.9973	.748	0.8468x + 3.3659	.134	.85
M_6	13.977x + 19.367	.727	-0.2251x + 4.377	.813	31.571x + 6.2169	.936	-0.2952x + 4.3068	.786	0.8933x + 2.9953	.179	.89
M_7	16.048x + 46.244	.423	-0.435x + 3.6912	.571	41.3x + 25.13	.706	-0.4617x + 3.5384	.512	0.7237x + 3.5538	.092	.72
M_8	18.589x + 37.536	.585	-0.5205x + 4.0314	.799	44.535x + 17.015	.846	-0.55x + 3.8696	.727	0.8321x + 3.4465	.125	.83
M_9	14.881x + 23.667	.681	-0.2607x + 4.3095	.788	34.273x + 8.8797	.911	-0.3315x + 4.2165	.753	0.8625x + 3.1251	.157	.86
M_{10}	17.473x + 36.68	.571	-0.4376x + 4.0471	.764	42.102x + 17.103	.836	-0.4838x + 3.8923	.698	0.809x + 3.4227	.120	.81
M_{11}	14.807x + 25.452	.650	-0.264x + 4.2766	.759	34.537x + 10.222	.891	-0.3334x + 4.175	.723	0.8425x + 3.1653	.148	.84

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 46cp. 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 sulpahte from its M_5 microcapsules was the most rapid followed by from that of M_{10} and M_{11} respectively. M_{10} 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 M_5 and M_{11}. The M_{11} microcapsules receive comparatively thick EC shells resulting comparatively slow SS release. Whereas the $t_{50\%}$ of M_5 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: M_{10} VS M_{11} and M_5 VS M_{11} as their $f_1 > 15.00$ and $f_2<50.00$. While M_{10} VS M_5 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 λ_{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

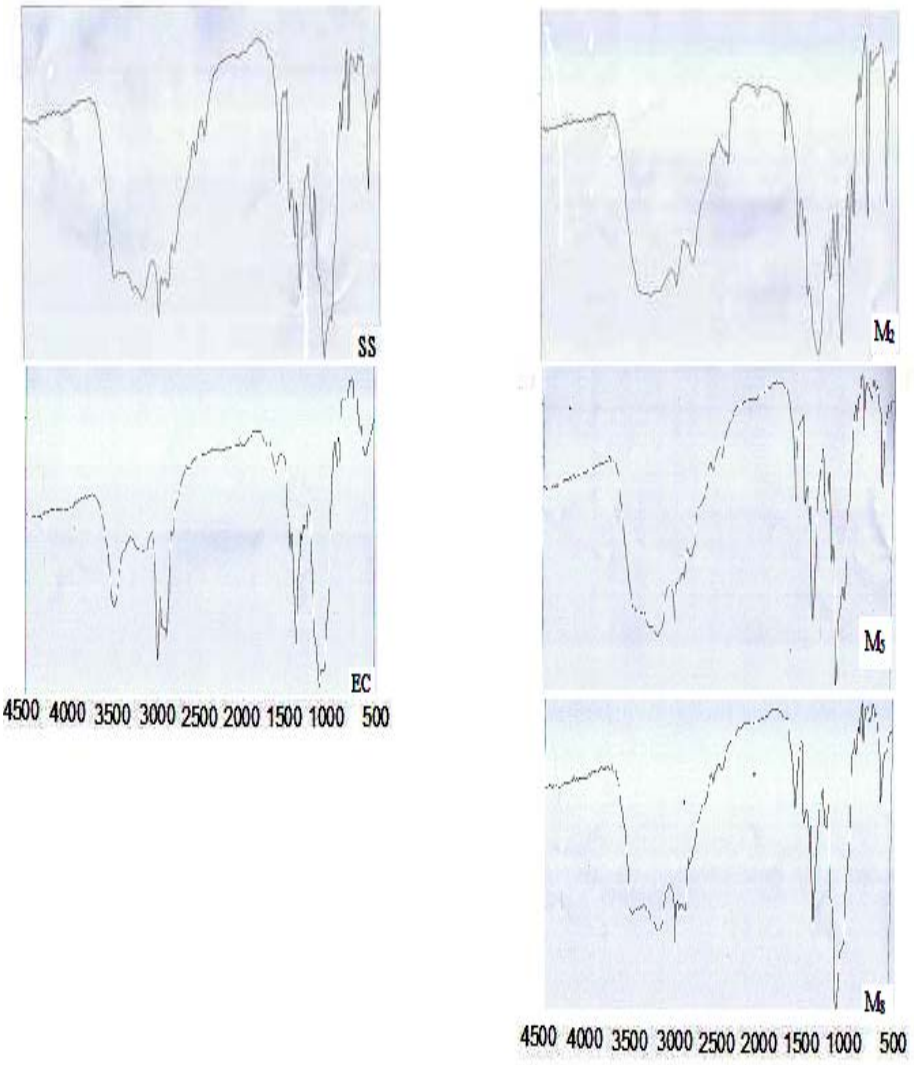

Fig. 4: FTIR spectras

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.

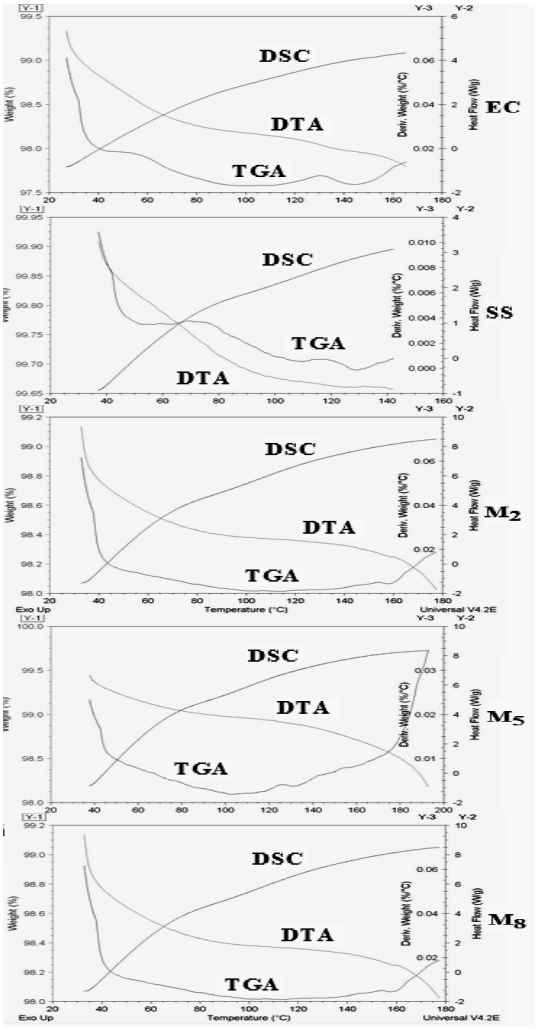

Fig. 5: Thermograms

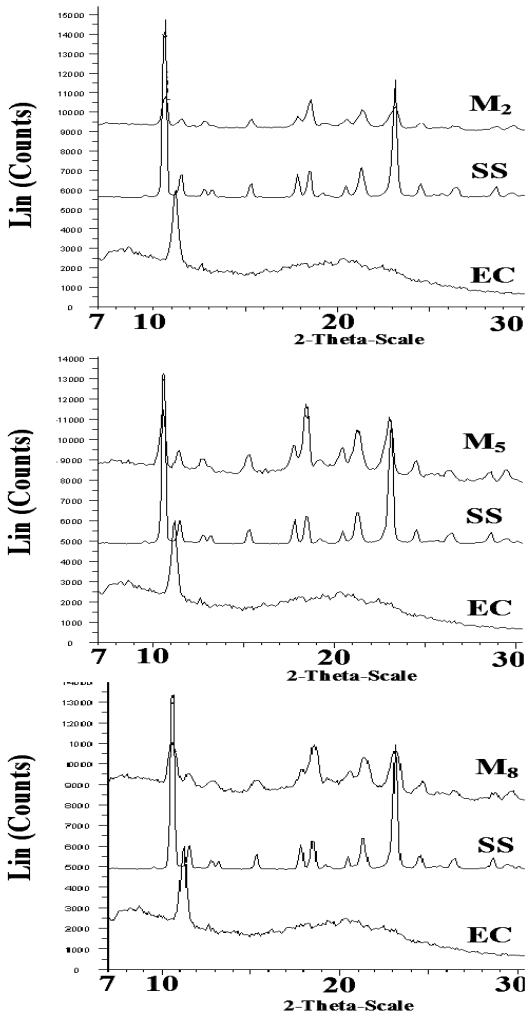

Fig. 6: X-ray diffractograms

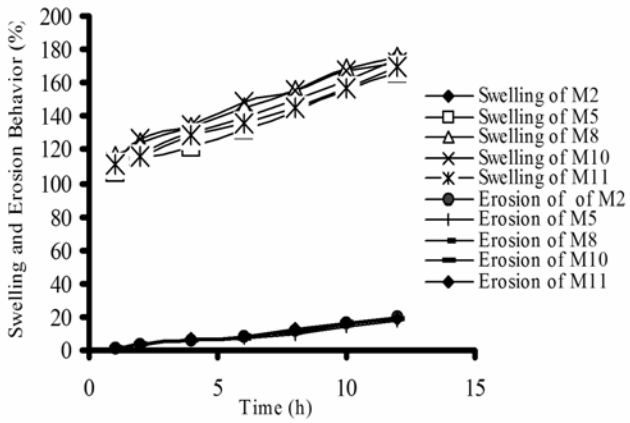

Fig. 7: Swelling (%) and erosion (%) behavior of various formulations

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 sulpahte 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 sulpahte at least twice in every 24 hours using ethylcellulose.

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