Salbutamol sulphate-ethylcellulose microparticles: formulation and in-vitro evaluation with emphasis on mathematical approaches

Murtaza G., *Ahmad A., Waheed Asghar A., Naeem Aamir M.

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

Received 28 May 2008; Revised 5 Oct 2008; Accepted 12 Oct 2008

ABSTRACT

Background and the purpose of the study: This study reports the laboratory optimization for the preparation of salbutamol sulphate-ethylcellulose microparticles by a non-solvent addition coacervation technique through adjustment of the ratio of salbutamol sulphate to ethylcellulose. The variation of drug release between the microparticles and tabletted microparticles was also investigated.

Methods: In vitro release profiles of developed microparticles and tabletted microparticles were studied using USP XXIV dissolution apparatus I and II, respectively, in 450 ml double distilled water at 50 rpm maintained at 37°C.

Results: White microparticles with no definite shape having good entrapment efficiency (96.68 to 97.83%) and production yield (97.48 ± 1.21 to 98.35 ± 1.08%) were obtained. In this investigation, initial burst effect was observed in the drug release behavior. The rate of drug release from microparticles decreased as the concentration of polyisobutylene was increased from 6% to 12% during microencapsulation. The release pattern of tabletted microparticles was affected significantly ($p < 0.05$) by the addition of hydroxy propyl methyl cellulose (HPMC) as excepient and insignificantly ($p > 0.05$) by the type of dissolution media and stirring speed. Tabletted microparticles showed good stability and reproducibility. Ethylcellulose was found to be compatible with salbutamol sulphate. The drug release from all formulations was best fit to Higuchi's equation and the mechanism of drug release was anomalous diffusion from all formulations.

Conclusion: The results of this study suggest that by using ethylcellulose it is possible to design a single-unit, sustained-release oral dosage form of salbutamol sulphate for indication of twice a day.

Keywords: Salbutamol Sulphate, Ethylcellulose, Non-solvent addition Coacervation, Dissolution.

INTRODUCTION

Patients with chronic diseases are increasing day by day. This situation necessitates the use of drugs for a longer period and taking a lot of medicines simultaneously, which may 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 methods to construct a formulation for delivering the drug in a controlled mode (1, 2). Microencapsulation involves the preparation of microparticles having a size range of 5-5000 μm (3).

Salbutamol sulphate (SS) 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 and its biological half life is about 4 to 6 hrs (4).

Ethylcellulose (EC) is a polymer of β-anhydro-glucose building blocks joined together by acetal bonding. It is generally considered as a nontoxic, biocompatible and non-biodegradable polymer. EC coated microparticles have also demonstrated their capability to absorb pressure and therefore save the coating from fracture during tablet manufacturing process. This process involves 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 (5, 6).

In the early projects, salbutamol sulphate was microencapsulated into various polymers by different techniques e.g. coacervation-thermal change and solvent evaporation (7, 8). The objective of the present work was to encapsulate SS by non-solvent addition-coacervation. The EC to SS ratios were varied as

Correspondence: ma786_786@yahoo.com

1:1, 1:2 and 1:3. The reproducibility and stability of tabletted microparticles were tested at different conditions. Their in vitro dissolution profiles were studied under different conditions and were evaluated physically and by the application of model-dependent and model-independent approaches.

EXPERIMENTAL

Materials

Salbutamol sulphate (Unexo Laboratories, Pakistan), Ethyl cellulose 22 cp (Sigma, USA), Toluene (Merck, Germany), Polyisobutylene (M.W. 2.800, Acros Organics, USA), Petroleum ether (40-60°C, BDH, England), Methanol (Merck, Germany), Distilled water (Instrumental laboratory, IUB, Pakistan). All other analytical grade chemicals were purchased from market sources.

Preparation of microparticles

Polyisobutylene (PIB, 6% w/w) was dissolved in an adequate quantity of toluene and to the resulting solution was added a weighed amount of EC with continuous stirring to make a homogenous EC solution. Then a specific amount of SS was dispersed gradually with stirring at 500 rpm to make a uniform mixture and after 15 min, about 200 ml petroleum ether (non-solvent) was added at a rate of 2-3 ml/min to induce phase separation. Addition of petroleum ether was continued and the system was cooled to 5 °C with ice for solidification of microparticles. Then 200 ml more chilled petroleum ether was added and the mixture was stirred for 2 hrs and the clear upper layer was separated by filtration. Microparticles were washed 2-3 times with 200 ml chilled petroleum ether. Finally, microparticles were refiltered, dried in air for 2 hrs followed by drying in vacuum oven (Memmert, Germany) at 50 °C for 4 hrs to remove residual solvents. This optimized method was applied to obtain reproducible yield of SS microparticles (10).

Physical Evaluation of microparticles

Mean diameter of microparticles was measured by using light microscope equipped with a microscope stage, a digital camera and a computer. The microparticles were suspended in water, placed on a glass slide and viewed under microscope. The photomicrographs were taken with digital camera to measure microparticle diameter by image analysis. The morphology of microparticles was determined by scanning electron microscope (10).

The percentage of microparticle solvation was obtained by following equation where M_1 is the weight immediately after microencapsulation and M_2 is weight after its drying to constant weight (9).

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

Density, compressibility index, hausnner's ratio and angle of repose were calculated according to the previous works (12, 13).

Tablet preparation

Salbutamol sulphate microparticles were mixed with 1% talc, 0.5% magnesium stearate and lactose and compressed into tablets (mean tablet weight ~ 200 mg) using single punch tablet machine (Emmay, Pakistan). Each tablet contained approximately 8 mg salbutamol. Three batches were prepared for each SS formulation.

Physical Evaluation of Tablets

The tabletted microparticles were evaluated with respect to weight variation, tablet hardness, friability and thickness (14).

Assay of Salbutamol sulphate

An accurately weighed quantity of microparticles and tabletted microparticles from each batch was treated as described previously (15) then analyzed spectrophotometrically at 276 nm, against its standard solution under the same conditions.

The entrapment efficiency was determined by the following equation:

$$\text{Entrapment efficiency (\%)} = \frac{\text{Amount of drug found in microparticles}}{\text{Amount of drug used for microencapsulation}} \times 100$$

The percentage production yield of the produced microparticles was calculated for each batch by dividing the weight of microparticles (M) by the total expected weight of SS and EC (M_t) (16, 17):

Production yield (%) = $M/M_t \times 100$

Each determination was performed in triplicate.

In vitro Dissolution Studies

The USP XXIV apparatus I (Pharma test, Germany) method was used for in vitro dissolution studies of microparticles in 450 ml distilled water at 50 rpm. An accurately weighed quantity of microparticles containing SS equivalent to 8 mg 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, Germany) at 0, 30, 60, 90, 120, 150 and 180 minutes with an automatic sample collector (Pharma Test, Germany). Each time 5 ml of the fresh dissolution medium was added to maintain a constant volume in the dissolution flask. The samples of SS were analyzed directly at 276 nm using a UV-Visible spectrophotometer (Shimadzu 1601, Japan). For in vitro dissolution study of various tabletted microparticles USP XXIV apparatus II (Pharma test, Germany) was employed and samples were drawn at pre-determined time intervals (0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hrs) after filtration through milli pore filters followed by UV spectrophotometeric analysis (18).

Process Variables

The influence of PIB on the release profile of SS microparticles was observed by varying its concentration as 6%, 9% and 12% during microencapsulation. Different ratios of HPMC (0%, 3% and 6%) were added as tablet excepient to study its influence on the release behavior of SS tabletted microparticles. Dissolution Media (Distilled water, 0.1M HCl and pH 6.8 Buffer) and stirring speed (50, 100 and 150 rpm) were also varied to study their influence on dissolution behavior.

UV and FTIR spectroscopy

Drug-polymer interaction was studied by UV spectroscopy in the range of 200-400 nm using UV-Visible spectrophotometer (Shimadzu 1601, Japan) (14). SS, EC and M_2 (optimum formulation) were also evaluated using FTIR spectroscopy (Shimadzu, Japan) (19).

Thermal analysis

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

X-ray diffractometry

X-ray powder diffractometric analysis of micro-particles 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.

Model analysis and Statistics

The methods which were employed to compare drug release profiles can be classified into two categories: model dependent and model independent approaches. Model-dependent approaches include Zero Order, First Order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas Kinetic Model and were employed to analyze dissolution data in this study (19).

ANOVA based procedures and pair wise procedures are the model independent approaches which were used in this research work. For this purpose, one way ANOVA plus Post-Hoc analysis (Duncan and Tukey) for significance at $P < 0.05$ was studied for release data using SPSS version 12.0 (20).

Batch Reproducibility and Stability on Storage

Three batches of tabletted microparticles with different SS & EC ratio were prepared and their dissolution rates were evaluated under the same conditions as given above. A particular number of tablets 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 tabletted microparticles were tested monthly for three months following the same procedure as previously described.

RESULTS AND DISCUSSION

The non solvent addition-coacervation technique was applied to prepare SS microparticles. Toluene was used as a solvent for EC, whereas SS is toluene insoluble drug. Petroleum ether was used as a non-solvent to induce coacervation. The microparticles were dried in air and oven to make sure of complete removal of toluene and petroleum ether as evident from solvation rate mentioned in table 1. EC was used as a shell-forming material on account of its safety, stability, hydrophobicity and compact film forming nature among water insoluble polymers (5). In this study the same active ingredients and polymer which was used as in the previous studies (7, 8) but a different encapsulation technique was employed. Previously, coacervation by heat change technique and solvent evaporation was employed respectively but in the present work, non-solvent addition coacervation technique was applied. Moreover, the former authors characterized microparticles only by dissolution but in this study, solvation, micromeritics, swelling and erosion, dissolution and drug-polymer interaction studies were employed to characterize microparticles. In addition, the study was concentrated on the effect of SS & EC ratio, PIB, HPMC, dissolution media and stirring speed on formulations. In the present study, an increase in solvation (%) was observed by increase in polymer concentration and decrease in PIB amount. Solvation is the ability of a solvent to make a homogeneous liquid solution with a solute through molecular interactions.

Physical Characterization of Microparticles

The microparticles were whitish, aggregated and irregular in shape. It is evident from figure 1 and table 1 that there is an increasing ($p > 0.05$) trend in particle size with an increase in EC concentration. Which may be attributed to the increase aggregation of EC particles with an increase in its concentration. Same observations were reported in previous studies (7, 8), while microparticle size of this study was lesser than that of reported previously (6). It was found that the encapsulation efficiency is influenced by core to wall ratio. With increasing EC ratio, more particles of SS are coated which leads to a higher encapsulation efficiency (27, 28). However, this increase was not significant ($p > 0.05$). An increase in EC concentration caused a slight increase in production yield of microparticles ($p > 0.05$). A little increase in encapsulation efficiency and production yield and slight decrease in particle size was observed by increase in PIB contents from 6%-12% during microencapsulation process ($p > 0.05$)

Table 1. Evaluation of physical characteristics of salbutamol sulphate microparticles.

Formulations	SS: EC ratio	PIB Conc. (% w/w)	Entrapment Efficiency (%)	Solvation (%)	Production yield (M±S.D) %	$t_{60\%}$ * (M±S.D) (hrs)
M_1	1:1	6	96.68	158.34	97.48 ± 1.21	0.85
M_2	1:2	6	96.98	176.09	98.19 ± 1.20	1.44
M_3	1:3	6	97.83	182.36	98.33 ± 1.37	2.93
M_4	1:2	9	97.01	172.85	98.14 ± 1.16	1.55
M_5	1:2	12	97.23	169.34	98.35 ± 1.08	1.72

* Time for 60% drug release

Table 2. Rheological properties of microparticles.

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°

as mentioned previously (10, 28). The encapsulation efficiency and production yield of present technique was better than the former methods (7, 8).

As given in table 2, there was a decrease in bulk density with the increase in polymer concentration. Such relationship between bulk density and polymer concentration has been reported previously. Compressibility index (less than 15%) indicated fine flow properties. Hausner's ratio (volume before taping/volume after taping), for all formulations, was below 1.29 again indicating free flow of all formulations of microparticles. Similarly angle of repose for all formulations were below 30° indicating once again free flowing nature of microparticles.

Physical Evaluation of Tablets

Physical parameters of the tablets were according to compendial requirements (Table 3). Tablet ranged from 8.3±1.2 to 9.5 ± 1.1 kg/cm^2. Friability was less than 0.5% (w/w). Weight variation was less than ±3.0 %. The mean thickness ranged from 3.87 to 3.89 mm.

In vitro dissolution studies

The formulations were passed through dissolution test and the obtained data was analyzed by various model independent analytical procedures. Time for 60% release of SS from M_1, M_2 and M_3 were 0.85, 1.44 and 2.93 hrs. Duncan test put $t_{60\%}$ values of all microcapsule formulations in an identical homogenous group while Tukey H.S.D. test proposed similarity of M_1 and M_2 data but both were insignificantly ($p > 0.05$) different from M_3 data. Each data set of following pairs of microcapsule formulations i.e. M_1 vs. M_3 and M_2 vs. M_3 showed different release pattern from its compared partner as their f_1>15.00 and f_2<50.00, whereas M_1 vs. M_2 had f_1<15.00 and f_2>50.00 showing similarity of compared profiles but to a very low extent.

It was observed that microparticles with higher EC concentration exhibited slower rate of drug release and vice versa. This result supports an assumption that microparticles with higher EC concentration have thicker polymer coating as compared to microparticles with lower EC concentration due to less number of surface pores in M_3 (Figure 2) confirming its slow drug release behavior. Moreover the use of higher EC concentration resulted in larger microparticles i.e. smaller surface area of microparticles in contact with dissolution medium resulting in slow drug release. Modified Noyes-Whitney equation also certifies this discussion (3):

$(dc/dt) = kS (Cs – Ct)$

Where dc/dt is the rate of dissolution, k is the dissolution rate constant, S is the surface area of dissolving body and Cs – Ct is the concentration gradient. Above mentioned results also revealed that the nature of drug changed from crystalline to amorphous during microencapsulation, since the amorphous form of a drug is usually more soluble than the crystalline form. Therefore, the release of drug from microparticles is quicker than other dosage form that satisfies immediate therapeutic effect. Moreover, it is reported previously that the release of hydrophilic drugs is mainly controlled by permeation through the water filled channels within the hydrophobic polymer (EC) membrane. These two etiologies are therefore responsible for slow diffusion of medium through the specific channels arguing decelerated rate of drug release from microparticles and tablets (8, 10, 25, $p < 0.05$, table 4). The corresponding data is presented in table 4. Although there is slight difference among different formulations with respect to their

Table 3. Evaluation of physical properties of salbutamol sulphate tabletted microparticles.

Formulations	Drug Contents (mg)	HPMC Conc. (%)	Weight Variation[a] (%) (±S.D) (n=20)	Thickness (mm) (M±S.D) (n=10)	Hardness (Kg/cm^2) (M±S.D) (n=10)	Friability (%) (n=10)	$t_{60\%}$** (hrs)
T_1	9.6 *	0	±2.8	3.88 ± 0.04	9.2 ± 1.3	0.36±0.2	4.78
T_2	9.6 *	0	±2.7	3.89 ± 0.03	8.5 ± 0.9	0.43±0.2	6.93
T_3	9.6 *	0	±2.1	3.88 ± 0.02	8.3 ± 1.2	0.29±0.3	11.05
T4	9.6 *	3	±2.2	3.87 ± 0.08	9.3 ± 1.5	0.39±0.2	8.13
T5	9.6 *	6	±2.1	3.89 ± 0.04	9.5 ± 1.1	0.44±0.4	11.93
Reference	9.6 *	Unknown	±1.4	3.87 ± 0.02	8.7 ± 0.7	0.31±0.1	7.57

[a] ± Maximum % variation from the arithmetic mean
* Equivalent to 8 mg Salbutamol
** Time for 60% drug release

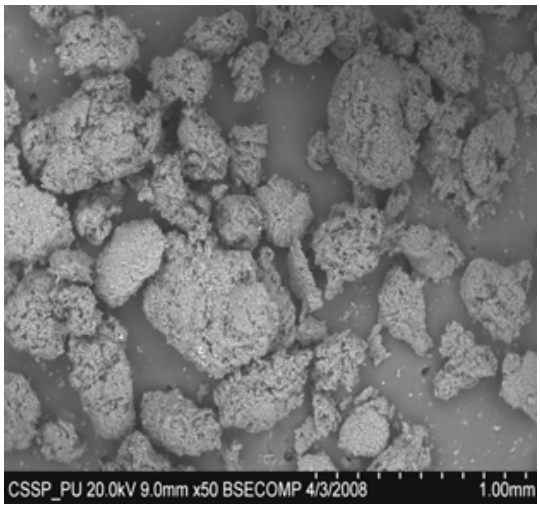

Figure 1. Scanning electron micrograph of M_1 formulation.

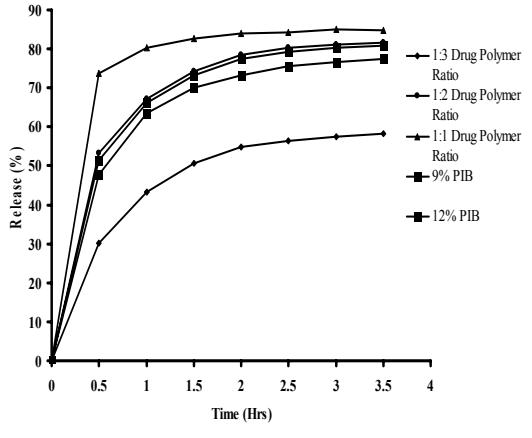

Figure 2. Dissolution profiles of salbutamol sulphate microparticles showing the effect of drug polymer ratio and PIB concentration on dissolution fashion.

entrapment efficiency but there is comparatively greater variation on the basis of their release kinetics. In this course, M_2 is the best formulation with optimum entrapment efficiency and release profile.

Dissolution curves consisted of two segments: initial part that indicates fast drug release in the start (desired for immediate therapeutic effect) and then tentatively a zero order plot segment that indicates a slow drug release (for prolonged effect). The formulation with 1:1 drug polymer ratio intensively quick drug release as compared to other two ratios. This result can be supported by an argument that it is the drug particles attached on the external surface of microparticles, responsible for initial rapid release and then subsequently slow drug release from the core of microparticles by diffusion. Such dissolution behavior is common in Biopharmaceutical Classification System Class I drugs i.e. salbutamol sulphate. (9, 28).

The kinetic analysis, on the basis of coefficient of determination R^2, approved higuchi model best fit to the dissolution data (Table 4 & 5) i.e. diffusion controlled drug release. Moreover, Korsemeyer-Peppas model showed anomalous mode (diffusion plus erosion) of drug release. Hixson-Crowell model elaborated a change in the surface area and diameter of the formulation with the progressive dissolution of the matrix as a function of time.

Batch reproducibility and stability on storage

No significant difference was observed in the release profiles of different batches of tabletted microparticles, indicating reliability and reproducibility of the manufacturing process ($p > 0.05$, f_1=0.29, f_2=99.71) which was employed. Also, the release kinetics remained unaltered for up to three months of storage, and there were no changes in the tablet characteristics suggesting that SS is stable in the tabletted microparticles for the above mentioned period. However, stability study for a more prolonged period should be conducted.

Influence of Process Variables

Statistical analysis shows that PIB concentration does not affect drug release behavior significantly ($p > 0.05$, f_1<15.00 and f_2>50.00). However, figure 2 shows a slight increase in sustaining effect on drug

Table 4. Release rate parameters of salbutamol sulphate from its microparticles.

Models	Formulations	T_1	T_2	T_3	T_4	T_5	Reference
	Y-equation	5.0685x + 35.772	5.468x + 22.117	4.418x + 11.164	5.3638x + 16.371	4.9022x + 10.526	5.6992x + 18.46
Zero Order	R^2	0.709	0.883	0.954	0.932	0.963	0.923
	r	0.842	0.940	0.977	0.965	0.981	0.961
	Y-equation	0.1615x + 3.0436	0.182x + 2.712	4.418x + 11.164	0.1911x + 2.5195	0.2028x + 2.2336	0.1909x + 2.6022
First Order	R^2	0.271	0.372	0 .484	0.430	0.515	0.414
	r	0.521	0.986	0.696	0.656	0.718	0.643
	Y-equation	2.795x + 18.56	2.8179x + 6.3263	2.1794x - 0.2247	20.872x + 1.8611	18.722x - 2.0925	2.8812x + 2.7876
Higuchi	R^2	0.907	0.986	0.975	0.988	0.984	0.991
	r	0.952	0.993	0.987	0.994	0.992	0.995
	Y-equation	-0.1517x + 4.0255	-0.143x + 4.3204	-0.0937x + 4.4887	0.2009x + 2.2636	0.2049x + 2.0003	0.2038x + 2.3455
Hixson-Crowell	R^2	0.976	0.994	0.992	0.508	0.577	0.497
	r	0.988	0.997	0.996	0.713	0.760	0.705
	Y-equation	0.6137x + 3.1039	0.6914x + 2.7802	0.7139x + 2.3484	0.7248x + 2.5923	0.7775x + 2.3022	0.7238x + 2.6755
Korsmeyer-peppa	R^2	0.261	0.358	0.451	0.412	0.505	0.397
	r	0.511	0.598	0.672	0.642	0.711	0.630
	n	.61	.69	.71	.72	.77	.72

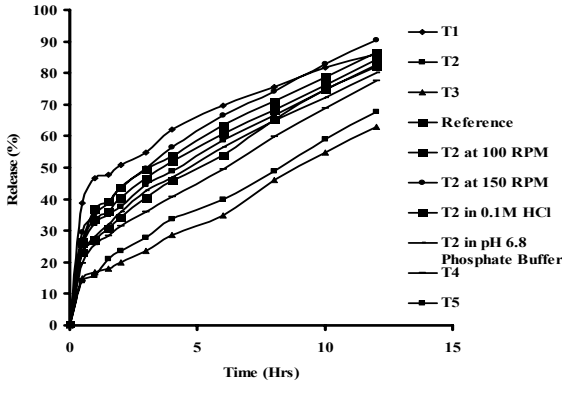

Figure 3. The dissolution profiles of salbutamol sulphate tabletted microparticles showing the effect of HPMC, stirring speed and type of dissolution media on dissolution fashion.

release from microparticles which can be attributed to the increased formation of numerous tiny discrete coated particles (10, 29). The use of HPMC as an excepient during tablet manufacturing process imposed a retardant effect on the drug release rate from tabletted microparticles due its binding effect ($p < 0.05$, f_1>15.00 and f_2<50.00). Almost similar pattern of SS release from tabletted microparticles was observed when dissolution medium was either distilled water or 0.1M HCl solution. A slight decrease in the rate of the dissolution was observed when phosphate buffer of pH 6.8 was used as dissolution medium ($p < 0.05$, f_1<15.00 and f_2>50.00). This result can be satisfied on the basis of the basic nature of drug as its solubility decreases with increase in pH. As it is shown in figure 3, the effect of stirring speed on in vitro dissolution was insignificant ($p > 0.05$, f_1<15.00 and f_2>50.00).

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 similar. 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 loaded microparticles. Some characteristic and prominent peaks of SS were observed in FTIR spectrum. The spectrum of the optimum formulation showed all the characteristic peaks of SS. Thus both spectrums precluded any strong SS-EC interaction when SS was encapsulated into EC coats.

Thermal analysis

Thermal analysis showed good stability of SS in the form of microparticles. The characteristic, well-recognizable thermal profile of the drug in a specific temperature range was observed. The same thermal behavior was observed in the case of its 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

The peaks present in diffractogram of pure drug prove its crystalline nature whereas amorphous nature of EC is evident from its diffractogram as there

Table 5. Release rate parameters of salbutamol sulphate from its tabletted microparticles.

Models	Formulations	M_1	M_2	M_3	M_4	M_5
Zero Order	Y-equation	15.723x + 44.274	17.965x + 33.09	13.977x + 19.367	17.98x + 32.107	17.278x + 30.322
	R^2	0.434	0.627	0.728	0.639	0.645
	r	0.659	0.792	0.853	0.799	0.803
First Order	Y-equation	0.760x + 2.5255	0.7979x + 2.3583	0.7747x + 2.0498	0.7999x + 2.3407	0.7945x + 2.3069
	R^2	0.357	0.411	0.464	0.416	0.420
	r	0.597	0.641	0.681	0.645	0.648
Higuchi	Y-equation	5.1976x + 23.829	5.4628x + 14.121	13.977x + 19.367	42.146x + 13.366	40.395x + 12.438
	R^2	0.717	0.877	0.728	0.885	0.889
	r	0.847	0.936	0.853	0.941	0.943
Hixson-Crowell	Y-equation	-0.4332x + 3.6203	-0.4858x + 3.9978	-0.2952x + 4.3068	0.8121x + 2.2215	0.8025x + 2.1792
	R^2	0.518	0.749	0.786	0.448	0.451
	r	0.720	0.865	0.887	0.669	0.672
Korsmeyer-peppa	Y-equation	0.7259x + 3.5222	0.8469x + 3.3658	0.8933x + 2.9953	0.8564x + 3.3473	0.8568x + 3.3039
	R^2	0.095	0.135	0.179	0.139	0.142
	r	0.308	0.367	0.423	0.373	0.377
	n	.73	.85	.89	.86	.86

is no characteristic peak. Moreover, diffractogram of microparticles contained specific peaks of drug and noise of EC which suggests that microparticles prepared by this method are a physical combination of SS and EC rather than chemical reaction.

CONCLUSION

This study elaborated that the non-solvent addition coacervation technique is an appropriate method to microencapsulate salbutamol sulpahte into the ethylcellulose coats. 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. No strong chemical interaction between drug and polymer was found. These results may suggest the potential application of ethylcellulose microparticles as a suitable sustained release drug delivery system. Therefore, by using ethylcellulose it is possible to formulate a single-unit, sustained-release oral dosage form of salbutamol sulpahte at least twice in every 24 hrs.

ACKNOWLEDGEMENT

The authors are very thankful to Unexo Laboratories for providing generously the sample of salbutamol sulpahte and Dr. Farhat Saleemi for the microcapsule characterization studies. We also thank the Research Fundation of Higher Education Commission, Pakistan for financial support given to this study.

REFERENCES

1. Yamuda T, Ohnishi H, Machida Y. Sustained release ketoprofen microparticles with ethylcellulose and carboxymethylethylcellulose. J Control Release, 2001; 75: 271-282.
2. Najafabadi AR, Vatanara AR, Gilani K, Tehrani MR. Formation of salbutamol sulphate microparticles using solution enhanced dispersion by supercritical carbon dioxide. DARU, 2005; 13: 2.
3. Bakan JA. Microencapsulation. Lachman L, Lieberman HA, Kanig JI. The theory and practice of industrial pharmacy. 2nd ed. Philadelphia; Lea & Febiger. 1986; 412-429.
4. Martindale-The Extra Pharmacopoeia. 33rd ed., Sean C Sweetman; 2002; 770-773.
5. Rowe RC, Sheskey RJ, Weller PJ. Handbook of pharmaceutical excepient. 4th Edition. 2003; 237-241.
6. Patel A, Ray S, Thakur RS. Invitro evaluation and optimization of controlled release floating drug delivery system of metformin hydrochloride. DARU, 2006; 14: 3.

7. Yazan Y, Demirel M, Guler E. Preparation and in vitro dissolution of salbutamol sulphate microcapsules and tabletted microcapsules. J Microencapsul, 1995; 12:601-607.
8. Amperiadou A, Georgarakis M. Controlled release salbutamol sulphate microcapsules prepared by emulsion solvent evaporation technique and study on the release affected parameters. Int J Pharm, 1995; 115:1-8.
9. Erden N, Celebi N. Factors influencing release of Salbutamol sulphate from poly (lactide-co-glycolide) microspheres prepared by water-in-oil-water emulsion technique. Int J Pharm, 1996; 137:57-66.
10. Barik BB, Ray S, Goswami N, Gupta BK, Ghosh LK. Preparation and in vitro dissolution of isoniazid from ethylcellulose microcapsules. J Acta Polo Pharm-Drug Res, 2001; 58:65-68.
11. Sah H. Microencapsulation techniques using ethyl acetate as disperse solvent: effects of its extraction rate on the characteristics of PLGA microspheres. J Control Release, 1997; 47:233-245.
12. Banker GS, Anderson NR. Tablets. Lachman L, Lieberman HA, Kanig JI. The theory and practice of industrial pharmacy. 2nd ed. Philadelphia; Lea & Febiger. 1987; 416-419.
13. Shariff A, Manna PK, Paranjothy KLK, Manjula M. Entrapment of andrographolide in cross linked alginate pellets: physicochemical characterization to study the pelletization of andrographolide. Pak J Pharm Sci, 2007; 20:1-9.
14. BP, 2004. Appendix XII G. Uniformity of Weight (Mass). London: British Pharmacopoeia Commission. P 1.
15. Sajeev C, Vinay G, Archna R, Saha RN. Oral controlled release formulation of diclofenac sodium by microencapsulation with ethylcellulose. J Microencapsul, 2002; 19:753-760.
16. Hascicek C, Gonul N, Erk N. Mucoadhesive microspheres containing gentamicin sulphate for nasal administration: Preparation and in vitro characterization. II Farmaco, 2003; 58:11-16.
17. Soppimath KS, Kulkarni AR, Aminabhavi TM. Encapsulation of antihypertensive drugs in cellulose-based matrix microspheres: Characterization and release kinetics of microspheres and tabletted microspheres. J Microencapsul, 2001; 18:397-409.
18. USP30-NF25, 2007. The official compendium of standards. The United States Pharmacopoeial Convention.
19. 18. Das MK, Rao KR. Microencapsulation of zidovudine by double emulsion solvent diffusion technique using ethylcellulose. Ind J Pharm sci, 2007; 69:244-250.
20. Khatun M, Islam SMA, Akter P, Quadir MA, Reza MS. Controlled release of Naproxen sodium from Eudragit RS100 Transdermal Film. Dhaka Uni J Pharm Sci, 2004; 3:1-10.
21. Higuchi T. Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci, 1963; 52:1145-1149.
22. Hixson AW, Crowell JH. Dependence of reaction velocity upon surface and agitation: I-theoretical consideration. Ind Eng Chem, 1931; 23:923-931.
23. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm, 1983; 15:25-35.
24. Koester LK, Ortega GG, Mayorga P, Bassani VL. Mathematical evaluation of in vitro release profiles of hydroxypropylmethylcellulose matrix tablets containing carbamazepine associated to β-cyclodextrin. European J Pharm and Biopharm, 2004; 58:177-179.
25. Polli JE, Rekhi GS, Shah VP. Methods to compare dissolution profiles. Drug Inform J, 1996; 30:1113-1120.
26. Al-Taani BM, Tashtoush BM. Effect of microenvironment pH of swellable and erodable buffered matrices on the release characteristics of diclofenac sodium. AAPS PharmSciTech, 2003; 4:E43.
27. Breghausen SW, Schote U, Frey M, Schmidt F. Comparison of microencapsulation techniques for the water soluble drugs nitenpyram and clomipramine HCl. J Control Release, 2002; 85:35-43.
28. Singh J, Robinson DH. Controlled release captopril microcapsules: effect of ethylcellulose viscosity grade on the in vitro dissolution from microcapsules and tabletted microcapsules. J Microencapsul, 1990; 7: 67-76.
29. SA B, Bandyopadhyay AK, Gupta BK. Effect of microcapsule size and polyisobutylene concentration on the release of theophylline from ethylcellulose microcapsules. J Microencapsul, 1996; 13:207-218.