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Preparation and *In-Vitro* Pharmacokinetic Evaluation of Compressed Kollidon® SR Based Salbutamol Sulphate Microcapsules: Effect of Pigments

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ABSTRACT

Microcapsules of salbutamol sulphate were prepared with kollidon® SR by W/O emulsification solvent evaporation technique using iron oxide yellow, iron oxide red and TiO_2 as pigments and light liquid paraffin oil was used as oil phase and 1% (w/w of the continuum) of span 60 as emulsifier. Salbutamol sulphate, a bronchodilator drug for asthma is suitable for designing as microcapsules to prolong its therapeutic duration. For the prepared microcapsules scanning electron microscopy (SEM) was performed to study the size and surface morphology of prepared microcapsules. UV-spectrophotometric method was applied to calculate the drug loading efficiency and the performance of the prepared dosage form was evaluated in terms of in-vitro dissolution studies according to USP XXX paddle method (type 2) in 400 ml distilled water (pH 7.4) for 8 hours at $37^0 \pm 5^0$ C temperature at 50 rpm. Release of salbutamol sulphate from the compressed microcapsules was found to follow Higuchi mechanism (R^2=0.99 and 0.99) when iron oxide yellow and iron oxide red were used in F-1 and F-2 respectively while F-3 followed both first order and Higuchi kinetic model (R^2=0.99) when TiO_2 was used. Korsmeyer equation was used to calculate the release exponent value (n) which indicates the drug release behavior and the mean dissolution time (MDT) for release rate where F-2 containing iron oxide red gave the highest value (4.12 h).

Key words: Salbutamol sulphate, kollidon® SR, sustained release, microcapsule, emulsion-solvent-evaporation technique.

INTRODUCTION

Rate programmed drug delivery plays a great role in predetermined duration of medication and has been increasing its high acceptability in advanced sustained release technology [1]. Patients

suffering from chronic discuses like asthma, diabetes and epilepsy may have to take drug every day for the rest of their life [2]. In management of chronic diseases like asthma, compliance to the dosage regimen is the key it a successful therapy. WHO estimated the number of asthmatic patients to be around to 150 million around the world [3].

Salbutamol sulphate belongs to the class called selective beta- 2 adrenergic stimulants. It is used in the management of asthma, chronic bronchitis and other bronco-pulmonary disorders involving bronchospasm [4]. In acute asthmatic conditions, salbutamol is given orally four times daily in a dose of 2.4 mg to maintain a therapeutic blood level. The biological half-life is about 4.5 h. Salbutamol sulphate is suitable for construction in an oral sustained release dosage from for 12-24 h [5]. In water and therefore the construction of a sustained release product in microcapsules is more convenient [6]. There are several methods available to formulate water soluble drugs into controlled release dosage forms [7]. Microencapsulation in a process used to control dough release and hence prolong therapeutic activity [8]. Sustained release microcapsules preparations in the frequency of dosing, decreased adverse reactions and improved patient compliance [9]. However, only few investigations appear in the literature about the use of compressed microcapsule into controlled release oral tablets [10-16].

The purpose of this investigation was (a) to prepare salbutamol sulphate microcapsule using kollidon® SR as rate retarding material by emulsion solvent evaporation technique; (b) to study the effect of pigments iron oxide red and iron oxide yellow on in-vitro dissolution and (d) to fit the data to various postulated drug release models.

MATERIALS AND METHODS

Salbutamol sulphate was gift from (Phramaraw, India), kollidon® SR and TiO_2 was collected from the regional office of (BASF, Germany) in Bangladesh, liquid paraffin oil light was of MERCK, Germany, iron Oxide yellow and iron oxide red was collected from Yixing City Yuxing Industry & Trade Co., Ltd, China and span 60 was from BDH Chemicals Ltd. England. All other chemicals or ingredients used in this study were of analysis grade.

Impact drill GSB 16RE (BOSCH, Germany), stirrer (Nipun, Bangladesh), UV-visible Spectrophotometer-1240 (Shiamdzu, Japan) for absorbance determination, Scanning Electron Microscope (SEM) S-3400 N (Hitachi, Japan), sonicator (POWER SONIC 505, HWASHIN TECHNOLOGY CO., Seoul, Korea), Tablet dissolution machine tester (USP Type III dissolution apparatus, VEEGO, INDIA) for dissolution and Perkin- Elmer compressor machine for tablet compression were used.

Preparation of salbutamol sulphate microcapsules

Microcapsules were prepared by an emulsification solvent evaporation technique [17]. Two batches were prepared with iron oxide yellow, iron oxide red and TiO_2 in an amount of 10% of total polymer content using 1% (w/w of the continuum) of span 60 as an emulsifier. Other ingredients were kept same for both the batches. (Table 1)

Table 1: Formulations and drug loading efficiency of microcapsules of salbutamol sulphate with kollidon® SR.

Formulation Code	Materials						Drug Loading (%)		
	SBS* (gm)	KSR** (gm)	Iron oxide yellow (gm)	Iron oxide red (gm)	TiO_2 (gm)	Methanol (ml)	Theoretic	Actual	Loading efficiency
F-1	2	1.8	0.2	-		10	50	48.52	97.04
F-2	2	1.8	-	0.2		10	50	49.75	99.50
F-3	2	1.8	-	-	0.2	10	50	49.14	98.28

**SBS= Salbutamol sulphate, **KSR= Kollidon® SR*

At first a kollidon® SR solution was prepared at a drug polymer ratio of 1:1 by dissolving kollidon® SR in methanol which acts as internal phase. Liquid paraffin oil was used as a vehicle and was emulsified with the help of stirrer at 3000 rpm and then salbutamol sulphate was dispersed in the emulsified external phase. A volume of previously prepared polymeric phase containing kollidon® SR was slowly added to the external phase and stirred for about 2 h keeping the same rpm. After 2 hrs the prepared microcapsules were washed by petroleum ether (40:60) and were allowed to dry in the natural air for about 2 or 3 days. The prepared microcapsules were then sieved, weighed and transferred to glass vials and stored in desiccators. Then the formulations were named as F-1, F-2 and F-3 for iron oxide yellow, iron oxide red and TiO_2 respectively.

Particle size analysis

Fractions of 132-370, 119-489, 61-330 μm of the prepared salbutamol sulphate microcapsules were separated for respective batches F-1, F-2,and F-3 by shaking using a set of standard sieves (British Standard). Selected fractions were used for in-vitro dissolution.

Assay of microcapsules

A few mg of kollidon® SR microcapsules containing salbutamol sulphate was taken in a mortar and was triturated properly until fine powder was formed. 30 mg of fine powder was taken in a 100 ml volumetric flask with the help of a funnel. Few ml of distilled water (pH 7.4) was added with the powdered microcapsules, sonicated for 30 minutes in a sonicator (POWER SONIC 505, HWASHIN TECHNOLOGY CO., Seoul, Korea.) to make a clear solution and then finally was filtered. Absorbance value was determined using UV spectrophotometer (UV mini-1240, SHIMADZU CORP., Kyoto, Japan) at a wave length of 276 nm. Using the absorbance value, the amount of salbutamol sulphate entrapped was determined with the help of standard curve.

The loading efficiency was assumed 50% for each batch. The data loading efficiency of each batch is represented in table 1.

Loading efficiency was calculated by using the following equation:

$$\text{Loading efficiency} = \frac{\text{Actual drug loading}}{\text{Theoretical drug loading}} \times 100$$

Preparation of compressed microcapsules

Compressed microcapsules were prepared according to table 2 by using the direct compression method. Hydroxypropyl methylcellulose (HPMC) 50 cps was used as a polymer for all the

formulations. The appropriate amount of microcapsule containing equal amount of salbutamol sulphate and HPMC were weighed and compressed on a single punch tablet machine (Perkin-Elmer laboratory hydrophilic press equipped with 13 mm faced punch and die set). The compression force and compression time were 5 ton and 30 seconds respectively. The final weights of compressed microcapsules were made to 300 mg.

Table 2: Formulation of compressed microcapsules of salbutamol sulphate with kollidon® SR.

Formulation Code	Amount of MC* (mg)	HPMC (mg)	Total weight (mg)
F-1	71	229	300
F-2	71	229	300
F-3	80	220	300

**MC= Microcapsule*

In-vitro dissolution study

In-vitro dissolution study was performed in a Paddle type Dissolution Apparatus (USP Type III Dissolution Apparatus, VEEGO, INDIA). 400 ml of Distilled water (pH 7.4) was used as dissolution media, paddle speed was set at 50 rpm, and temperature was maintained fixed at 37ºC. The compressed microcapsule of each batch was transfer in each dissolution basket. The dissolution process was carried out for 8 hour and 10 ml dissolution sample from each batch was withdrawn at predetermined intervals (15 min, 30 min, 45 min, 60 min, 120 min, 180 min, 240 min, 300 min, 360 min, 420 min and 480 min). Each and every time 10 ml dissolution sample was compensated by fresh 10 ml distilled water. Dissolution samples were withdrawn with the help of 12 ml syringe and were kept airtight in a test-tube (screw cap). The dissolution samples were then analyzed spectrophotometrically in a UV-VIS spectrophotometer (UV mini-1240, SHIMADZU CORP., Kyoto, Japan) at a wave length of 276 nm. The dissolution study for each batch was performed in triplicate.

Scanning electron microscopy (SEM)

Surface nature of the microspheres was examined with the help of Scanning Electron Microscope (S-3400N, Hitachi). The microspheres were dried completely before examination. SEM was done at different magnifications of 15.0 kv X 25 SE, 15.0 kv X 100 SE, 15.0 kv X 500 SE and 15.0 kv X 2.00k SE.

RESULTS AND DISCUSSION

Salbutamol sulphate microcapsules were successfully obtained with kollidon® SR using iron oxide yellow, iron oxide red and TiO_2 in a size ranging from ≤61-489 µm and the drug content in the prepared microcapsules ranged from 97 to 98 % of the theoretical content for the three batches, indicating high incorporation efficiency.

Scanning electron microscopic analysis

The pigments were used at a concentration of 10% to the polymer content. The solvent system and surfactant was constant as described above. Spherical shaped with one or two big pores were seen in case of F-1. Rest of the surface was smooth and contour (figure 1). The pores may helped the dissolution media into the polymer matrix and leak out the drug. But due to insufficient number of pores the formulation gave intermediate drug release rate (9.21 mg/h) which was

calculated from zero-order curve shown in the table 3. In the case of F-2 the surface was more regular, smooth and continuous in nature (figure 1) with spherical and cylindrical shaped. The surface was also more compact blocking the pores on the polymer surface which might be the cause to have the lowest drug release rate (K=8.74 mg/h).

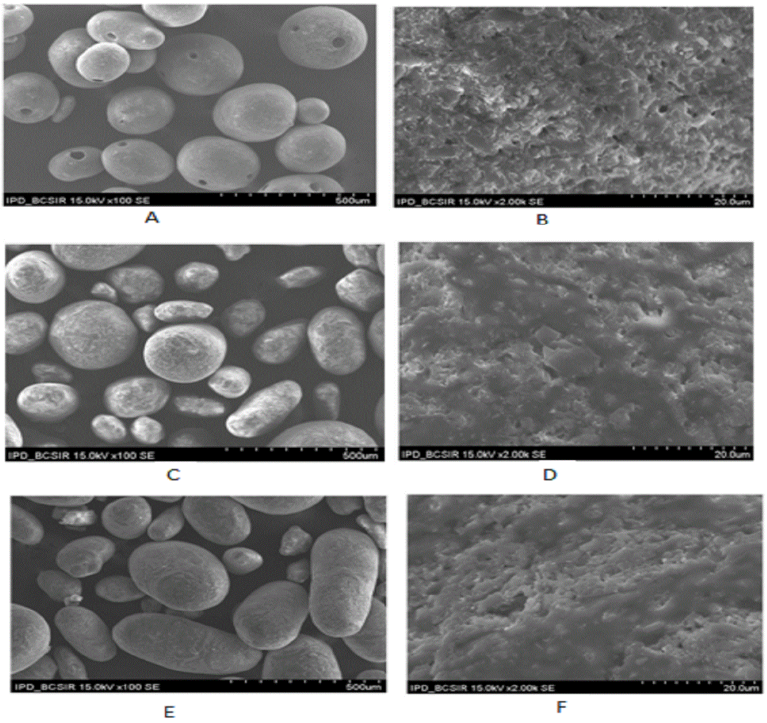

Fig. 1. Scanning electron microscopic picture of F-1 to F-3.
A and B represents 15.0 kv×100SE and 15.0kv×2.00k SE magnification for F-1 while C,D and E,F represents the similar respective magnification for F-2 and F-3 respectively.

When TiO_2 was used in F-3 it was practically insoluble in water they deposited on the surface of the polymer matrix as observed in the in the figure 1. It was the compression force that might cause more compact surface by mechanical interlocking mechanism and ultimately resulted in intermediate drug release pattern of F-3 where the MDT value was 3.07 h as shown in table 3.

In vitro dissolution study and release characteristics

The effect of different pigments on the release profile of salbutamol sulphate is explained in the Fig: 2(a), where 70% drug release secured at around 5 h for F-1, nearly 6 h for F-2 and 4.5 h for F-3 respectively.

After 2 h the initial burst release was seen for all the batches about 45.78%, 44.33% and 50.34% accordingly. Almost similar release found in case of F-1 and F-2 up to 6 h of dissolution study. The formulation F-1 was found to give faster drug release of 97.74% while F-2 was slower (77.81%) among the three after 8 h of experiment.

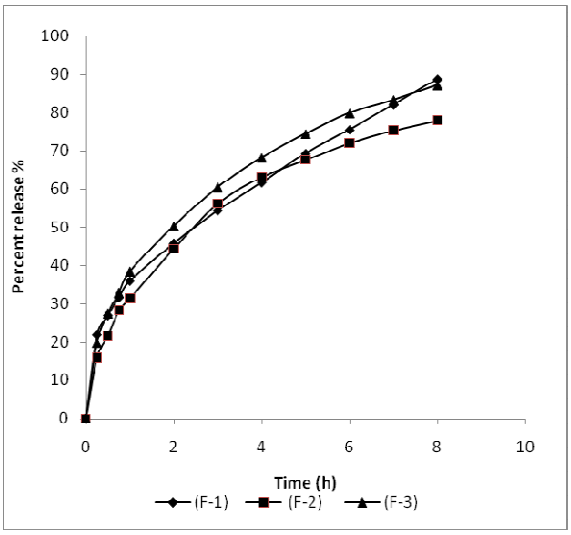

Fig. 2(a). Zero order release of salbutamol sulphate

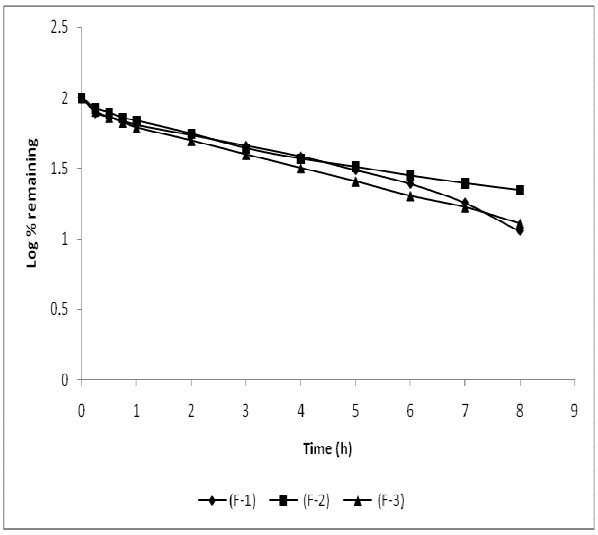

Fig. 2(b). First order release of salbutamol sulphate

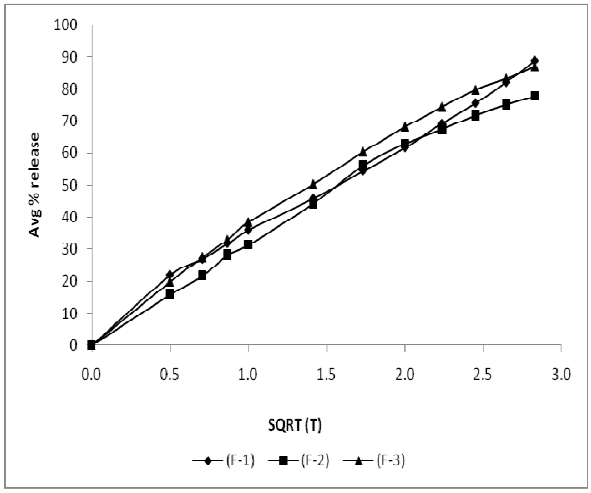

Fig. 2(c). Higuchi release pattern of salbutamol sulphate

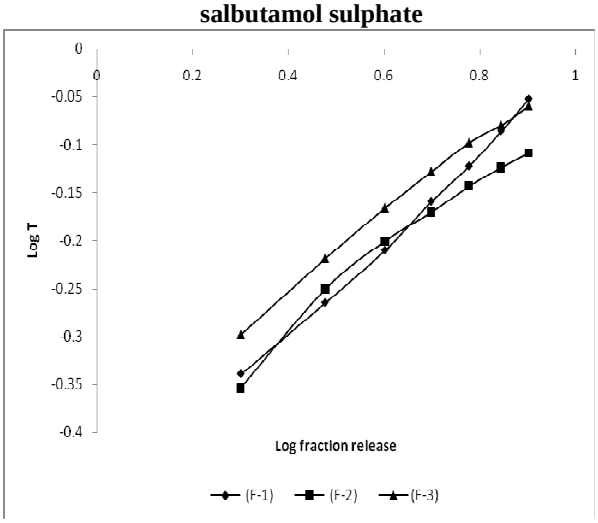

Fig. 2(d). Korsmeyer release pattern of salbutamol sulphate

The slope values (zero order rate constants, K) were obtained from straight line portion of the figure 2(a) were 9.21, 8.74 and 9.38 in percent release versus time plots for the formulations of batches F-1, F-2, and F-3 respectively. Figure 3 indicates the release rate of salbutamol sulphate from each batch.

In order to obtain meaningful information for the release, the drug release data were fitted to various kinetic models zero-order, first-order, Higuchi and Korsmeyer. Table 3 summarizes the correlation coefficient (R) for the different release kinetic models of theophylline microspheres. Models with higher R^2 values were judged to be more appropriate models for the release data. The linear relationship between the logarithms of the percentage drug remained to be released from the microspheres as well as the relationship between the amount of theophylline released and square root of time, indicated that the drug release appeared to fit either first order or Higuchi diffusion model.

Korsmeyer equation was used to calculate the release exponent (*n*) and mean dissolution time (MDT). Korsmeyer et.al and Peppas presented a simple semiemperical equation which can be used to analyze data of controlled release of water soluble drugs from the polymers. [18, 19]. The general form of this equation is:

$$M_t/M_\infty=K_t^n$$

Where, M_t/M_∞ is the fraction released by the drug at time t. K is a constant incorporating structural and geometric characteristic and n is the release exponent characteristic for the drug transport mechanism.

El-Bagory et al [20] used this equation to evaluate the drug release mechanism from ethyl cellulose microspheres. According to the mathematical modeling slab, sphere, cylinder or matrix disc, the values of diffusion n=1, when release process is exactly zero order process, a case II transport and 0.5<n<1 would be a non-fickian diffusion, where 0.43<n<0.5 is known as fickian diffusion.

Higher R^2 values for Higuchi diffusion model were observed for F-1 and F-2 (0.99 and 0.99) while F-3 was best fitted with both first order and Higuchi model as shown in table 3. The values of n was equals 0.50, 0.33 and 0.37 which confirms non-fickian diffusion for F-1 and fickian diffusion for rest of the batches.

Table 3: Correlation co-efficient (R^2), release rate (K), release exponent (*n*) and MDT value of different formulations of salbutamol sulphate from kollidon® SR microcapsules using different pigments

Formulation Code	Zero order		First order		Higuchi		*n*	MDT
	R^2	K	R^2	K	R^2	K		
F-1	0.92	9.21	0.98	-0.10	0.99	29.29	0.50	3.46
F-2	0.92	8.74	0.98	-0.08	0.99	28.25	0.33	4.12
F-3	0.89	9.38	0.99	-0.10	0.99	30.38	0.37	3.07

The mean dissolution time (MDT) was calculated from Korsmeyer equation to characterize the drug release rate. Highest MDT value 4.12 h was observed in case of F-2 prepared with iron oxide red while lowest for the formulation containing TiO_2 which is presented in table 3.

CONCLUSION

The microcapsules of kollidon® SR with salbutamol sulphate were prepared successfully by (W/O) emulsion solvent evaporation technique using three different pigments. Very few efforts have been reported on the application of widely used matrix polymer kollidon® SR for microcapsule preparation. The drug release pattern was found satisfactory with pigment substances which directly affected the release kinetics. The drug release was significantly lowered in case of iron oxide red. As polyvinyl acetate and polyvinyl pyrrolidon (Povidone) based matrix polymer (Kollidon® SR) has already been established as a sustained release polymer [21] it can be useful as well for microcapsule preparation. But more study is required with kollidon® SR for microencapsulation technology.

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