WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 7, 1533-1548. Research Article ISSN 2277– 7105

GATRORETENTIVE NANOPARTICLES OF AN ANTI-ASTHMATIC DRUG: DEVELOPMENT AND CHARACTERIZATION

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Article Received on
25 April 2020,

Revised on 15 May 2020,
Accepted on 04 June 2020,

DOI: 10.20959/wjpr20207-17784

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ABSTRACT

Introduction: Asthma is one of the most common chronic and non-communicable diseases in children and adults effecting more than 300 million people worldwide. Intravenous, oral, or inhalation are the common route of drug administration in asthmas. The drugs with high absorption in gastrointestinal tract (GIT) have short half-lives therefore quickly eliminated from the systemic circulation; hence need frequent administration of drug to attain required therapeutic response. **Objective:** The objective of this research is to develop a novel drug delivery system to prolong gastric retention so that an effective drug concentration can be maintained in the systemic circulation for an extended period of time after oral administration. **Method:** The nano-precipitation technique was used to formulate nanoparticles so that the toxic effect of chlorinated solvents and surfactants can be eliminated. The hydrophilic polymers like bovine serum albumin, chitosan, and gelatin were used in two drug-polymer ratio (i.e. 1:1 and 2:1) for the preparation of Salbutamol sulphate nanoparticles. The formulated nanoparticles were then evaluated for percentage yield, particle size, surface morphology, drug entrapment efficiency, drug loading efficacy, swelling index, mucoadhesive strength and drug release profile. **Results & discussion:** The drug and polymer compatibility study shows no major interaction between the drug and polymers. The formulated nanoparticles of Salbutamol with different polymers concentration have shown percentage yield in the range of 72.35± 0.13 % to 86.88± 0.19 %, Drug loading efficacy in the range of 11.19 ± 0.4 % to 31.15 ± 0.8 %, whereas the entrapment efficacy was found in between 54.81±2.9 % and 85.82±4.2 % particle size in the range 287.45±09 nm to 894.06±28nm. Based on results the formulation SNN 2 has been selected as optimised formulation. **Conclusion:** The formulated Gastro retentive nanoparticles offer many potential advantages like efficient drug delivery; maximizing absorption and enhancing absolute

bioavailability with maximum benefit to patient.

KEYWORDS: Nanoparticles, Asthma, Salbutamol, gastroretentive, Anti-asthmatic, nano-precipitation,

INTRODUCTION

The annual global asthma occurrence is rising drastically from last few decades, at present, more than 339 million people are suffering from asthma worldwide, and the major contributors are low-and lower-middle income countries.[1] Asthma or Bronchial asthma is a long-term disease of the lungs, caused by inflammation and narrowing of lungs which make breathing difficult, coughing, wheezing, shortness of breath and chest tightness. Asthma is classified on the basis of severity and occurrence.[2-4] Though asthma do not have any specific treatment due to its complex pathogenesis, only long-term consistent treatments can only reduce and control the symptoms by reducing attacks and improve the prognosis Figure 1. Corticosteroid inhalation is the common treatment most of the asthmatic patients respond well. The first-line control strategy for asthma is combinations of steroids with bronchodilators for example long- or short-acting beta-receptor agonists (LABA or SABA) or leukotriene receptor antagonists (LTRAs) are considered best.[5] The fact is even after the administration of the maximum dose of corticosteroids the asthma control is still poor in some asthmatic patients.[5] Importantly, the cost of asthma related medicines increases by 60% due to poor response of the drug inpatients.[6] The human monoclonal antibodies and cytokine/chemokine antagonists are also used along with inhaled glucocorticoids to treat moderate to severe refractory asthma, but these approaches also gain limited success due to the heterogeneity of diseases.[7-9]

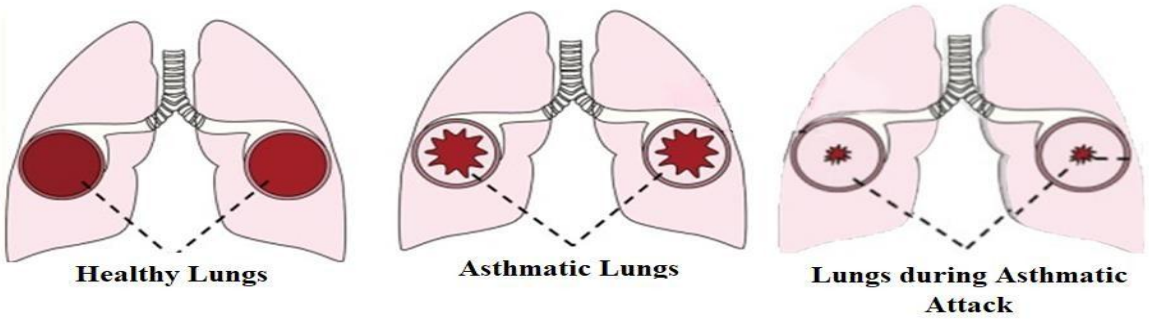

Figure 1: Human lungs.

Salbutamol sulfate a short-acting beta-2 agonist with a plasma half-life of 4-6 hr is most commonly used to treat diseases such as asthma, emphysema and bronchitis. Due to short

half-life the recommended dose of salbutamol sulphate for adults and children is usually given every 4 to 6 h.[10, 11] The maximum of salbutamol sulphate oral dose of 5 mg, hence there is a need to develop a novel drug delivery system to enhance bioavailability of drug and to improve patient compliance.[12,13] The formulated nanoparticles may provide the prolonged release of drug due to high water solubility of salbutamol sulfate so that the dose frequency reduced and side effects as well the fluctuation of drug plasma concentration can be minimised.

Gastro-retentive drug delivery System (GDDS) is site specific drug delivery system it delivers the drugs either in stomach or in intestine. The dosage form is retained in stomach by increasing the gastric retention of drugs, like intra-gastric floating systems, hydro dynamically balanced systems, extendable or expandable, microsponges system, micro-balloons, bio/mucoadhesive systems, high-density systems, and super porous biodegradable hydro gel systems.[14] GDDS is used to maximize the therapeutic index of the drug and also for reduction in the side effects.

Nanotechnology is an extensive field of research, manipulates and controls atoms and molecules sized 0.1–100 nm and produced relevant materials or structures.[15] It is an important and powerful tool for the development of biomedicine, including the diagnosis, treatment, and prevention of diseases.

The purpose of this research was to develop a gastroretentive drug delivery system using nanotechnology to deliver the drug to the absorption site at a controlled rate so that the oral bioavailability of the drug can be enhanced. An anti-asthmatic drug Salbutamol sulfate was used as active ingredient along with mucoadhesive polymers like bovine serum albumin, chitosan, and gelatin, to prepare gastroretentive nanoparticles. The mucoadhesive polymer used in the study increases the contact of dosage form at the site of absorption and reduces the luminal diffusion pathway of the drug (bioadhesion).[16] This will enhance the residence time of the dosage form on mucosal tissues in the stomach and improves absorption of the drug and increase the drug bioavailability.

MATERIALS AND METHOD

Materials

Salbutamol sulphate was obtained from Salius Pharma Pvt. Ltd. Navi Mumbai, Maharashtra India, Bovine serum albumin (BSA), and gelatin were obtained as a gift sample from

Modern Laboratories (Indore, India); chitosan was obtained as a gift sample from Indian Sea Foods (Cochin, India). Other chemicals and reagents used were of analytical grade.

Method

Drug and excipients compatibility studies

The Drug and excipients compatibility study was carried out by IR spectroscopy of the drug and excipients individually as well as in physical mixture using Fourier-Transform Infrared spectroscopy (FTIR) scanning measurement range of 400-4000 cm-1 and the resolution was 2 cm-1.and Differential Scanning Calorimetry (DSC) spectral analysis analysis was performed at a rate 5.00ºC/min from 50°C to 200ºC temperature range under nitrogen flow of 25 mL/min.[17, 18]

Preparation of Nanoparticles

Nano-precipitation technique was implemented in the preparation of nanoparticle.[19] A total of 6 formulations were prepared using drug polymer ratio 1:1 & 1:2. The polymers used in the formulations were bovine serum albumin, chitosan and gelatin. An accurately weighed quantity of polymer was dissolved in measured quantity of acetone (Solution A). The accurately weighed amount of drug was dissolved in required quantity of dichloromethane separately (Solution B). The solutions A & B were mixed and to the mixture 50 ml of water was added and stirred for a 30 min using magnetic stirrer. Acetone was eliminated by evaporation under reduced pressure using rotary flash evaporator and the final volume of the suspension was adjusted to 10 ml. Then this suspension was centrifuged using refrigerated centrifuge on 15000 rpm at 4ºC for 30 min. The supernatant was discarded and precipitate was washed thrice with distilled water. The nanoparticles thus obtained were dried overnight in oven at 60ºC, packed in self-sealing pouches and stored in a desiccator for further use.

Characterization of Prepared Nanoparticles Percentage Yield

Percentage yield is the proportion of actual theoretical yield and the experimental yield obtained. Usually the percentage yield is always less due to incomplete reaction or the loss of product during recovery. The percentage yield was calculated using equation (Eq. 1).

$$\text{Percentage Yield} = \frac{\text{Amount of nanoparticles collected}}{\text{Total amount of the polymer and drug}} X100 \qquad \text{Eq. 01}$$

Drug loading Efficiency

Drug content or the drug loading efficacy of the formulated nanoparticles was determined by removing the drug from the nanoparticles by extraction process using 0.1 M hydrochloric acid. The exactly weighed (50 mg) of formulated nanoparticle was stirred in 50 ml of 0.1 M hydrochloric acid until dissolved with the help of a magnetic stirrer, the solution was filtered through a Millipore filter and the drug content was determined after suitable dilution, at 276 nm spectrophotometrically. The % loading efficiency of the nanoparticles was calculated according to Equation (Eq. 2)

$$\text{Drug Loading Efficacy} = \frac{\text{weight of nanoparticles}}{\text{Amount of drug present in the nanoparticles}} X100$$

Eq. 02

Drug entrapment efficiency

A weighed quantity of formulated nanoparticles equivalent to 100 mg of the pure drug were crushed to powder using mortar & pestle and 100 ml phosphate buffer (pH 7.4) was added. The solution obtained was stirring vigorously using magnetic stirrer for 2 h. The solution was then filtered through Whatmann filter paper no 40. 1ml of this solution was diluted using phosphate buffer (pH 7.4) and the drug contents was determined spectrophotometrically at 276 nm.[20] The drug entrapment efficiency was determined using Equation (Eq. 3).

$$\text{Drug Entrapment efficiency} = \frac{\text{Experimental drug content}}{\text{Theoritacal drug content}} X100$$

Eq. 03

Fourier-transform infrared spectroscopy (FT-IR)

The formulated nanoparticles were subjected FTIR spectroscopy to identify any drug-polymer interactions during preparation technique. 17) The recorded spectra were compared with spectra recorded for pure drug and drug- excipients. The samples were prepared in KBr disks and recorded in scanning range was 400-4000 $cm^{-1}$and the resolution was 2 cm^{-1}.

Differential scanning calorimetry (DSC)

The differential scanning calorimetry analysis of pure drug and drug loaded nanoparticles were performed to asses any possible drug-polymer interaction. The analysis was performed at a rate 5.00ºC/min from 50°C to 200ºC temperature range under nitrogen flow of

2ml/min.17.

Surface Morphology

The morphology and surface characteristics of prepared nanoparticle formulations were determined after coating the product with gold in an argon atmosphere. The surface morphology of the microspheres was then studied by scanning electron microscope.

Particle size measurement

Malvern Zetasizer was used to determine the particle size of the formulated nanoparticles. Glass cuvette were used for the purpose, the 3/4th cuvette was with filled with organic solvent and formulated nanoparticles and ultra- sonicated and were used for the measurement of particle size.[21]

Swelling Index

Phosphate buffer (pH 7.4) was prepared freshly for the purpose and used to determine of swelling capacity of the nanoparticles, Baseline measurements and after incubation with phosphate buffer for 0.25, 0.50, 1.0, 2.0, 4.0, 0.6, 8.0, 10.0 and 12.0 hrs. The swelling index was measured using microscopy techniques. The extent of nanoparticle swelling at different time interval was determined by difference in particle diameter at time given time and the initial diameter of the prepare nanoparticles using equation (Eq. 4).

$$\text{Percentage Swelling Index} = \frac{\text{Diameter of nanoparticles at a specific time}}{\text{Initial diameter of the nanoparticles}} X100 \quad \text{Eq. 04}$$

Mucoadhesive properties

To evaluate the mucoadhesive characteristics of formulated nanoparticles in vitro wash-off method was implemented.[22, 23] To determine the mucoadhesive strength of the formulated nanoparticles an artificial biological flow was stimulated to wash test product fixed to a mucous membrane. To perform the study a 10 cm ^{2} freshly cut goat stomach mucosa was obtained and cleaned thoroughly in isotonic saline solution. The mucosa membrane was tied onto a glass slide with the help of a thread and a weighed quantity of prepared nanoparticles was spread over the mucous membrane. The relative humidity was maintained at 85% for 30 min. using desiccator during the entire study. Freshly prepared Phosphate buffer solution (pH 7.4) was allowed to fall over the mucosa at a flow rate of 10 ml/min using a peristaltic pump

for 2 hr. The difference between the applied nanoparticles and flowed nanoparticles was then calculated using Equation (Eq. 5)

$$\text{Mucoadhesive Strength} = \frac{\text{Amount of Nanoparticles Adher to membrane}}{\text{Initial amount nanoparticles applied to membrane}} X100$$

Eq. 05

***In-vitro* drug release**

In-vitro release study[24-27] of the formulated nanoparticles was performed USP XXIV six station dissolution apparatus type 1 (basket). The dissolution chamber was filled with 900 ml of freshly prepared phosphate buffer (pH 7.4) used as dissolution medium. An accurately weighed amount of the salbutamol sulfate nanoparticles was placed into the basket assembly. The study was carried out at 100 rpm and constant temperature of 37 ± 1°C was maintained. A 2 ml sample were withdrawn and replaced by an equal volume of fresh pre-heated dissolution medium at specific time intervals. The sample withdrawn was filtered using whattman filter paper no. 40 and after suitable dilution, the samples were analysed at 276 nm spectrophotometrically. The concentrations of salbutamol sulphate in samples calculated and a graph was plotted between time and % cumulative release.

RESULTS AND DISCUSSION

The identification, purity of drug and drug – excipient compatibility studies was performed using FTIR and DSC. The FTIR spectra and DSC graph of pure drug and physical mixture of drug and excipients were recorded and compared to identify specific peaks by virtue of respective functional groups present in their chemical structures and no change in the peaks of functional groups was reported Figure 1 & 2.

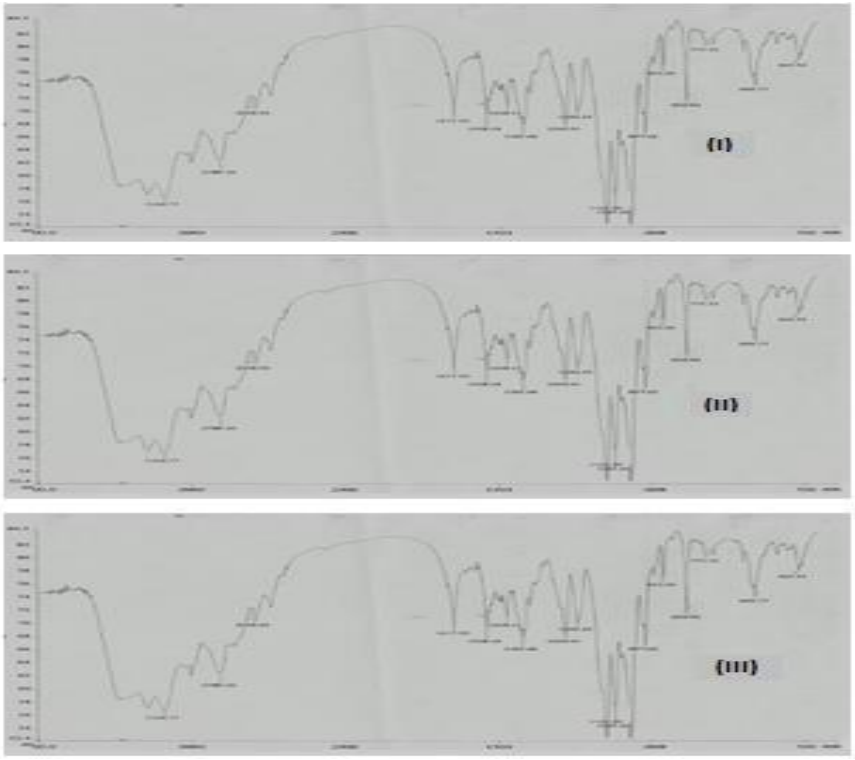

Figure 1: FT-IR spectrum of (I) Pure drug (II) Drug + Excipients and (III) Prepared nanoparticles.

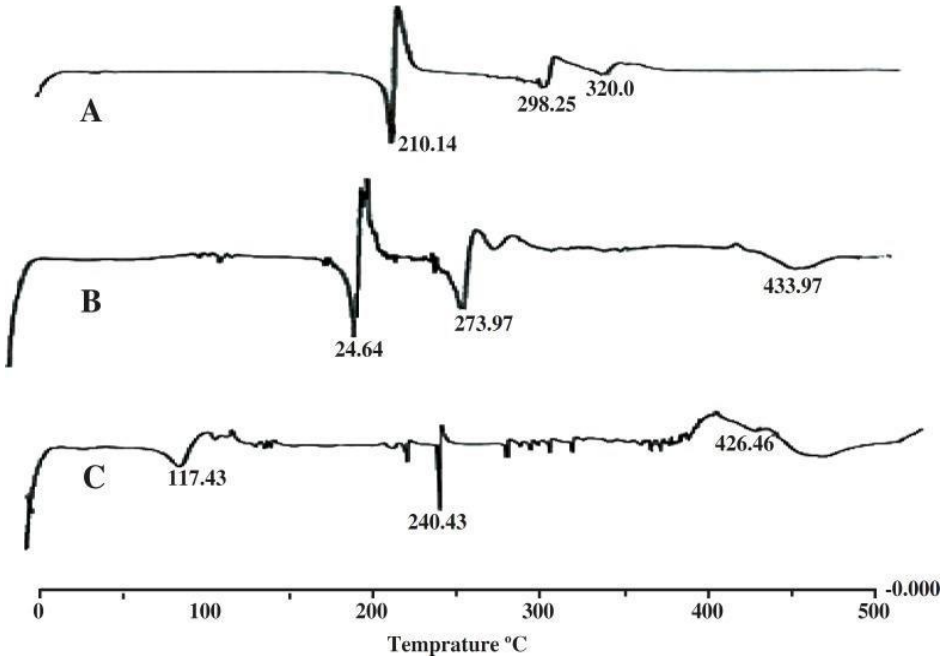

Figure 2: DSC thermograph of (a) Pure drug, (b) Drug + Excipients and (C) Prepared nanoparticles.

The salbutamol sulfate nanoparticles were prepared by nano-precipitation technique a total of 6 formulations was prepared as per composition Table 1.

Table 1: Formulae used for preparation of salbutamol nanoparticles.

Composition	Formulation Code					
	SSN 1	SSN 2	SSN 3	SSN 4	SSN 5	SSN 6
Salbutamol sulfate (mg)	100	100	100	100	100	100
Bovine serum albumin (mg)	100	--	--	200	--	--
Chitosan (mg)	--	100	--	--	200	--
Gelatine (mg)	--	--	100	--	--	200
Dichloromethane (ml)	5	5	5	5	5	5
Acetone (ml)	25	25	25	25	25	25
Distilled water (ml)	50	50	50	50	50	50

The formulated salbutamol sulfate nanoparticles were then evaluated for the various physico-chemical parameters. The percentage yield was found to be in the range of 72.35± 0.13% to 86.88± 0.19%. While drug loading demonstrate the amount of salbutamol sulfate encapsulated in to the amount of nanoparticles and it was found to be in a range of 11.19 ± 0.4% to 31.15 ± 0.8%, The entrapment efficiency of the polymer used is the ratio of the theoretically assumed amount of drug and the actual amount entrapped drug in the prepared nanoparticles formulations. The formulated nanoparticles of salbutamol sulfate were shown a drug entrapment efficacy between 54.81±2.9% and 85.82±4.2% range. The polymer-drug combination and the method used for the preparation of nanoparticles are the two important factors decide the Loading efficacy of the drug. It was seen that the hydrophobic polymers demonstrate higher encapsulation efficacy of hydro phobic drugs, where hydrophilic polymers encapsulate good amounts of hydrophilic drugs. The drug entrapment efficacy of the polymer can also be influenced by emulsifier type used, drug-polymer ratio, and the polarity of the liquid phase used. In Current study it was observed that the Albumin and gelatine represents the low drug loading and entrapment efficacy, while chitosan shows highest drug loading and entrapment efficacy formulation SSN 2 Table 2.

The performance of the nanoparticles is completely dependent on two important factors i.e. the particle size and particle size distribution, since the formulation with extensive particle size distribution indicated significant deviations in drug absorption on the site, drug release, bioavailability and efficiency. Particle size and particle size distribution were determined using scanning electron microscopy (SEM). The particle size of the formulated nanoparticles was found in the range of 287.45±09 nm to 894.06±28nm. The particle size increases with the increase in drug-polymer ratio. The particle size distribution pattern, describe that the, minor portion range from 24.8% to 36.8% and major portion from 75.2% to 93.8%. The particle size for minor and major portion lies between 19 nm to 740nm and 200nm to 1250nm

respectively Table 2 Figure 3.

Table 2: Characterization of salbutamol sulfate nanoparticles.

Formulation Code	Parameter					
	Yield ± SD %	DLE*# ± SD %	DDE* # ± SD %	MPS* # (nm) ± SD	PSD*	MS* # (hr)
SSN 1	78.45 ± 0.23	27.82 ± 0.5	62.84 ±5.4	287.45 ±09	24.8% (19-32 nm) 75.2%(200 – 410 nm)	7.12 ± 07
SSN 2	86.88 ± 0.19	31.15 ± 0.8	85.82 ±4.2	324.12 ±13	6.2% (50-84 nm) 93.8% (225-530 nm)	11.42 ± 03
SSN 3	82.47 ± 0.20	12.48 ± 0.2	76.53 ±3.6	632.18 ±16	18.3% (65 -170 nm) 81.7% (430-1180 nm)	6.26 ± 05
SSN 4	72.35 ± 0.13	11.19 ± 0.4	54.81 ±2.9	784.07 ±23	34.2% (280-640 nm) 65.8% (660-1200 nm)	9.36 ± 08
SSN 5	84.51 ± 0.23	18.28 ± 0.5	80.12 ±5.8	485.04 ±31	21.2% (90-280 nm) 78.8% (400-1100 nm)	14.45 ± 02
SSN 6	68.54 ± 0.26	12.36 ± 0.6	68.28 ±7.6	894.06 ±28	36.8% (320-740 nm) 63.2% (520-1250 nm)	8.54 ± 08

*= DLE= Drug Loading efficacy, DEE=Drug Entrapment Efficacy, MPS=Mean Particle Size, PSD=Particle Size Distribution, MS= Mucoadhesive Strength # = Average of three determinations.

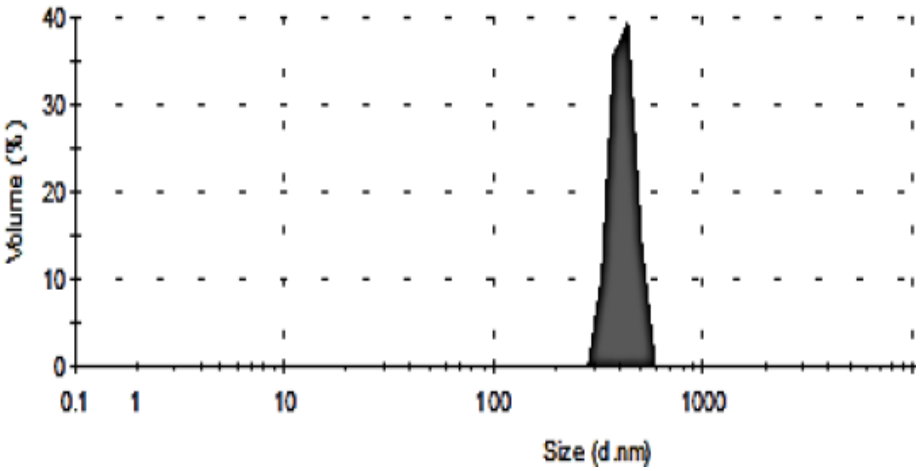

Figure 3: Particle size distribution of formulated nanoparticles.

The wash-off method used to determine the mucoadhesion indicated the greater mucoadhesive strength of nanoparticles ranging from 7.12 ± 07hr to 14.45± 02hr during ex vivo studies Table 2. The strong adhesive bonding between the mucus membrane and the nanoparticles is due to the electrostatic forces and hydrogen bonding. The gastro retention and drug release into the GIT was made possible due to the unique mucoadhesive properties of the nanoparticles. The swelling profile of nanoparticles formulations at different time

intervals was recorded. The findings indicate that the soaking of the nanoparticles in phosphate buffer solution at pH 7.4 was taken place rapidly. As expected, the capillary action was used to withdraw water from the underlying mucosa which is a tendency of formulated mucoadhesive nanoparticles this helps in rapid swelling ensuing stronger adhesion. The swelling index of nanoparticles was found in the range from 184.7% to 293.4% in 12hr Table 3 and Figure 3.

Table 3: % swelling of salbutamol sulfate nanoparticles.

Time (hr)	Swelling Index (%)*					
Formulation Code	SSN 1	SSN 2	SSN 3	SSN 4	SSN 5	SSN 6
0.25	10.2	24.7	9.6	32.5	42.8	29.8
0.5	21.8	45.9	18.2	54.8	86.5	53.6
1	45.6	92.5	37.9	97.4	128.6	91.8
2	80.4	134.6	62.5	147.2	174.5	132.9
4	154.2	190.3	118.3	191.8	208.6	163.4
6	180.9	231.5	152.7	227.9	264.8	196.2
8	190.6	250.7	162.8	256.3	296.1	226.4
10	210.8	266.4	176.9	280.7	318.7	267.3
12	224.7	276.2	184.7	293.4	334.5	286.6

* = Average of ten determinations.

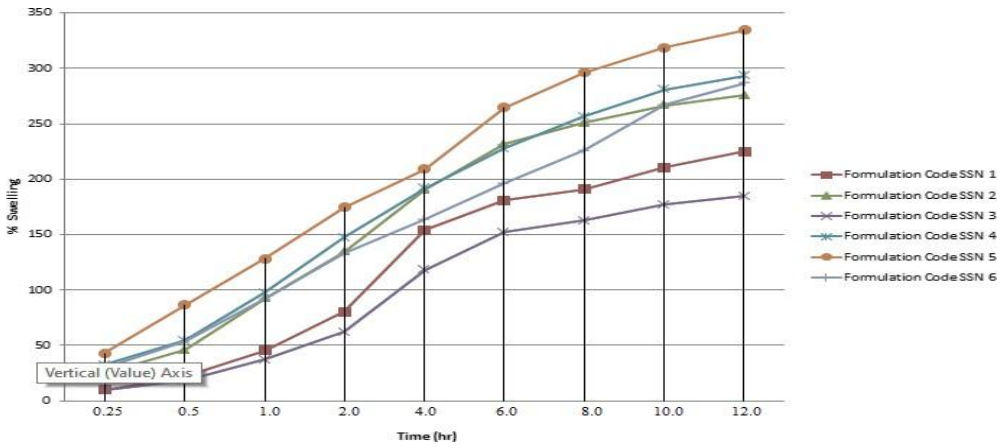

Figure 3: Swelling Index of salbutamol sulfate nanoparticles.

The nanoparticles prepared by nano-precipitation technique revealed smooth to minor wrinkled surfaces (Figure 4) maybe due to contractions throughout the drying process in the during the preparation.

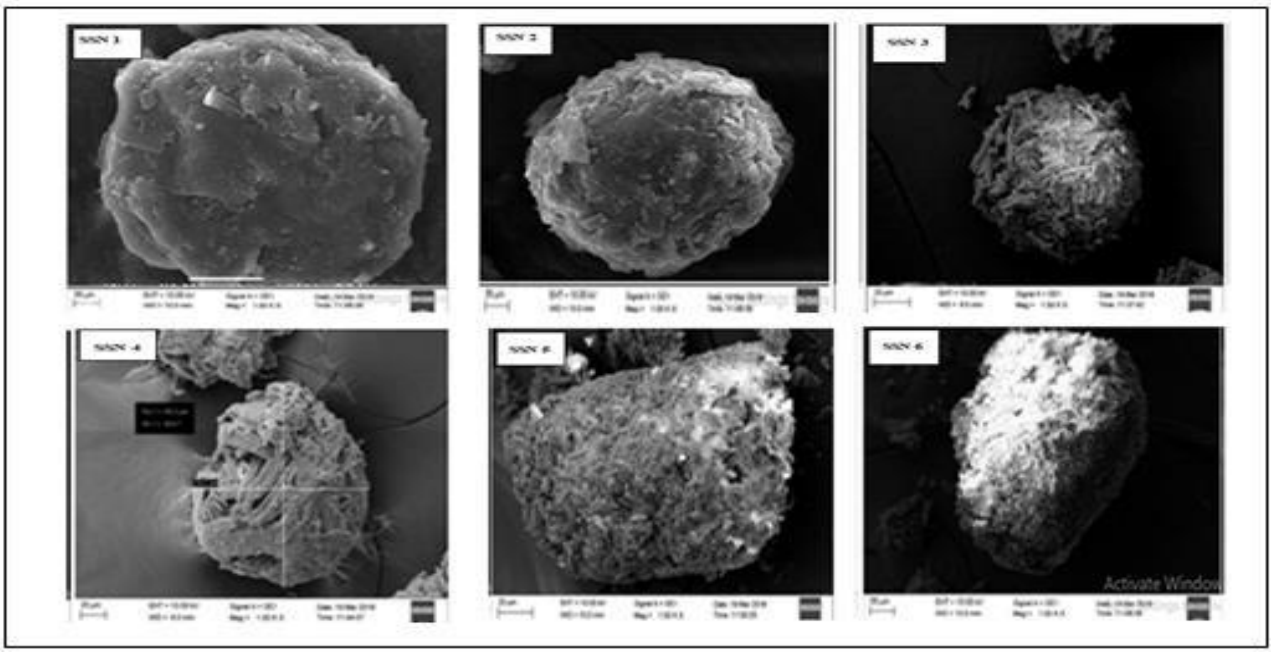

Figure 4: Surface morphology of formulated salbutamol sulfate nanoparticles.

Drug release study

It was observed during *in-vitro* drug release study that when the concentration of the polymer in the system increased the release rate of salbutamol sulphate decreased. It indicates that this may be due to the presence of drug particles adhered on the surface of the nanoparticles. The decreased significantly when the drug to polymer ratio was increased from 1:1 to 1:2, burst effect of salbutamol sulphate released from the nanoparticle formulation. The ideal release profile was observed in formulation with drug-polymer ratio of 1:1. The release profiles of different batches were recorded in Table 4 and Figure 5. The findings represent that an increase in the polymer concentration produced nanoparticles with reduced porosity due to the higher polymer binding rate. It was also understood that higher concentration of polymer provides prolonged drug release due to longer diffusional path length. Hence the increased polymer-drug ratio thickens the polymeric barrier which slows the entry of dissolution medium in to the nanoparticles therefore less quantity of drug release out from the drug-polymer matrix and responsible for prolonged release.

Table 4: Drug release behaviour of formulated salbutamol sulfate nanoparticles.

Time (hr)	% cumulative Drug release					
	SSN 1	SSN 2	SSN 3	SSN 4	SSN 5	SSN 6
0.25	11.98	7.45	5.84	2.25	1.98	2.37
0.5	20.45	15.86	9.45	3.75	2.56	3.86
1	29.46	26.18	14.89	8.46	6.01	7.96
2	38.38	35.95	24.68	16.85	9.63	14.26
3	46.83	46.24	32.45	31.56	13.48	23.65
4	54.08	59.65	39.56	42.68	19.61	29.64
5	60.87	65.14	45.89	51.25	23.67	34.52
6	67.45	73.01	54.8	63.56	29.35	41.86
7	71.46	79.12	61.51	68.96	47.89	49.48
8	78.76	83.51	68.19	74.26	56.43	56.32
9	82.46	88.97	73.57	79.85	61.06	63.68
10	85.74	91.85	85.45	82.36	68.95	69.92
11	89.66	95.14	87.84	86.54	73.87	74.23
12	93.56	98.56	93.78	88.56	79.23	76.57

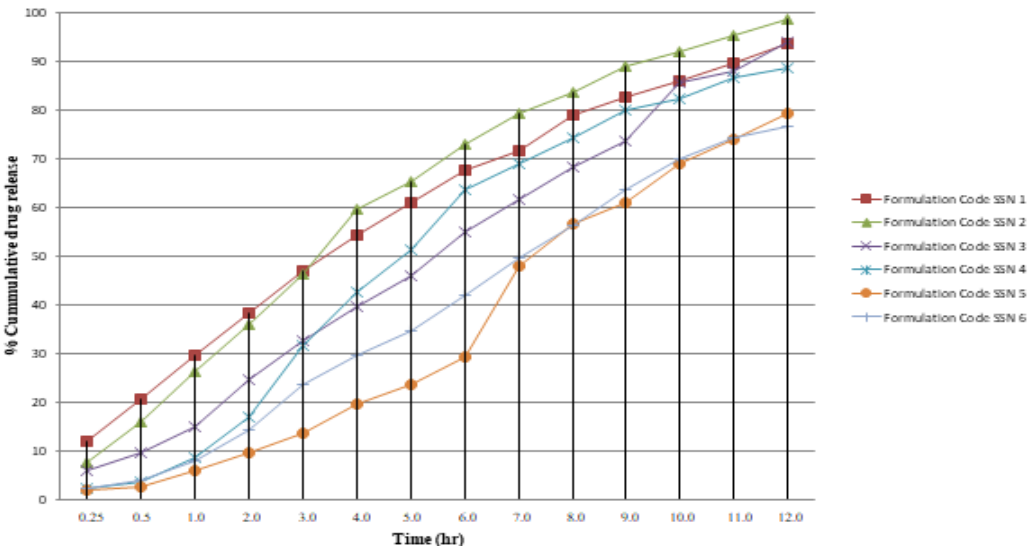

Figure 5: A plot % cumulative drug release vs time for formulated nanoparticles.

CONCLUSION

Salbutamol sulphate nanoparticles were successfully prepared using all the three polymers at a drug-polymer ratio of 1:1 and 1:2 by nano-precipitation technique. On the basis of various physico-chemical parameters and in-vitro drug release profile it was concluded that the formulation SSN 2 with drug-polymer ration of 1:1 was found to be highly suitable for the development of nanoparticle of salbutamol sulfate and show various advantages over conventional oral dosage form of same drug such as enhanced absorption and bioavailability.

ACKNOWLEDGEMENT

The author thanks, Department of Pharmaceutics, Mar Dioscorus College of Pharmacy, Sreekariyam, Thiruvananthapuram, Kerala, and Maa Pharmaceuticals and Research Center, Ajmer, Rajasthan, for providing required facilities and support to carry out this research work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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