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FORMULATION DEVELOPMENT AND EVALUATION OF MUCOADHESIVE MICRO-SPHERES OF SALBUTAMOL SULPHATE BY USING A NATURAL POLYMER

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ABSTRACT: Salbutamol sulphate (SS) loaded microspheres were prepared by solvent evaporation method with combination of *Sterculia foetida* gum in various proportions. A total of eighteen formulations were prepared in different oil phases i.e., liquid paraffin and sunflower oil. Those prepared from liquid paraffin L1-L9 and those prepared from sunflower oil were S1-S9. Based on the particle size, entrapment efficiency, drug content,% yield, swelling index, % moisture loss, micromeritic properties batches prepared from sunflower oil showed better results as compared to those microspheres prepared from liquid paraffin. Thus, sunflower oil batches were optimized for further evaluation parameters. From further parameters four formulations were selected i.e., S2, S6, S8, S9. It was confirmed with the results of micromeritic property that all the selected formulations showed good flow property. Release data were analyzed based on best fitting models and all the optimized batches showed good fit to first order, Higuchi kinetics and Korsemeyer-Peppas. Stability studies showed almost negligible changes in particle size, drug content and drug release throughout the study period.

INTRODUCTION: Novel drug delivery systems [NDDS] that can precisely control the release rate or target drugs to a specific body site have had an enormous impact on the healthcare system. Microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier characteristics. However, the success of these novel drug delivery systems is limited due to their short residence time at the site of absorption.

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It would, therefore, be advantageous to have means for providing an intimate contact of the novel drug delivery systems with absorbing membranes. Coupling mucoadhesion characteristics to microspheres and developing novel delivery systems as mucoadhesive microspheres can achieve it [1].

Mucoadhesive drug delivery systems are one of the novel drug delivery system, which utilize the property of bioadhesion of polymers that become adhesive on hydration [2]. These drug delivery systems can be used for targeting a drug to a particular region of the body for extended period of time [3]. Bioadhesion is an interfacial phenomenon in which two materials, at least one of which is biological, are held together by means of interfacial forces [4].

The attachment could be between an artificial material and biological substrate such as adhesion between a polymer and biological membrane. In case of polymer attached to the mucin layer of mucosal tissue, the term mucoadhesion is used. Mucoadhesive materials have been investigated and identified [5]. These are generally hydrophilic macromolecules that contain numerous hydrogen bond forming groups (e.g. hydroxyl and carboxyl groups) and will hydrate and swell when placed in contact with water.

In most cases these materials require wetting to become adhesive. However, over hydration may result in the formation of slippery mucilage and a loss of adhesive properties. Mucoadhesive microspheres include microparticles and microcapsules (having a core of the drug) of 1-1000μm in diameter and consisting either entirely of a mucoadhesive polymer or having an outer coating of it, respectively [6].

Microspheres in general, have the potential to be used for targeted and controlled release drug delivery but coupling of mucoadhesive properties to microspheres as additional advantages e.g. efficient absorption and enhanced bioavailability of the drugs due to high surface to volume ratio, a much more intimate contact with the mucus layer. Mucoadhesive microspheres can be tailored to adhere any mucosal tissue including those found in eye, nasal cavity, urinary and gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of drugs. Various natural polymers have been used for preparing mucoadhesive microspheres.

Microspheres provide sustained release over a prolonged period of time and better bioavailability than conventional dosage forms which reduces dosing frequency, side effects and thereby increases patient compliance. The smaller size and spherical shape of microspheres increases the surface area which increases the bioavailability of the dosage form. It also has advantage over the microparticles and nano particles as they tend to accumulate at the site of action but microspheres due to its smaller size (i.e. micron size) and spherical shape can be injected and hence shows better bio-availability. Microspheres are defined as spherical microscopic particles having a size range of 1- 1000μm.

Salbutamol sulphate is a short acting beta–adrenergic agonist with more bronchodilatory effect and less cardiac stimulatory effect and useful in the treatment of bronchial asthma. Salbutamol sulphate is readily absorbed from gastrointestinal tract. The plasma half-life of Salbutamol sulphate varies from 2 to 7 hours. In the treatment of asthma, it is given in the dose of 2-4mg, three to four times a day orally.

MATERIALS AND METHODS: Salbutamol sulphate was obtained as a gift sample from Supriya Lifesciences Ltd., Mumbai. *Sterculia foetida* gum and sunflower oil was purchased from the local market. Liquid paraffin and Span 20 was obtained from Loba Chemicals, Mumbai. All other reagents used were of analytical grade.

Preparation of salbutamol sulphate microspheres using *Sterculia foetida* gum as a natural polymer: Microspheres were prepared by water in oil emulsification solvent evaporation technique. A polymeric aqueous solution was made adding drug and the polymer and then the solution poured into 100 ml of light liquid paraffin containing 0.5% span-20 as an emulsifying agent. The aqueous phase was emulsified in oily phase by stirring the system in a 500ml beaker. Constant stirring at 500-1000 rpm was carried out using mechanical stirrer. The beaker and its content were heated at 250^{o}C using heating mantle, stirring and heating were maintained for 2.5 hrs. The aqueous phase was evaporated. The microspheres were washed with Iso-propyl alcohol or n-hexane, separated and dried at room temperature. The same procedure was done by changing the oil phase by sunflower oil.

Total 18 batches were prepared, 9 batches with liquid paraffin oil phase and 9 batches with sunflower oil phase with different drug: polymer ratios . For all batches RPM and temperature were maintained constant. All the batches were selected for optimization and evaluated.

Constant stirring at 500-1000 rpm was carried out using mechanical stirrer. The beaker and its content were heated at 25^{o}C using heating mantle; stirring and heating were maintained for 2.5 hrs. The aqueous phase was evaporated. The microspheres were washed with Iso-propyl alcohol or n-hexane, separated and dried at room temperature.

The same procedure was done by changing the oil phase by sunflower oil. Total 18 batches were prepared, 9 batches with liquid paraffin oil phase and 9 batches with sunflower oil phase with different drug: polymer ratios. For all batches RPM and temperature were maintained constant. All the batches were selected for optimization and evaluated.

TABLE 1: COMPOSITION OF SALBUTAMOL SULPHATE MICROSPHERES IN LIQUID PARAFFIN OIL PHASE

LIQUID PARAFFIN				
Sr. no	**Formulation code**	**Salbutamol sulphate (%w/v)**	***Sterculia foetida* gum (%w/v)**	**Tween 80**
1	LP 1	1	3	(0.5%)
2	LP 2	1	2	(0.5%)
3	LP 3	1	2.5	(0.5%)
4	LP 4	2	3	(0.5%)
5	LP 5	2	2	(0.5%)
6	LP 6	2	2.5	(0.5%)
7	LP 7	3	3	(0.5%)
8	LP 8	3	2	(0.5%)
9	LP 9	3	2.5	(0.5%)

TABLE 2: COMPOSITION OF SALBUTAMOL SULPHATE MICROSPHERES IN SUNFLOWER OIL PHASE

SUNFLOWER OIL				
Sr. no.	**Formulation code**	**Salbutamol sulphate (%w/v)**	***Sterculia foetida* gum (%w/v)**	**Tween 80**
1	SF 1	1	1.5	(0.5%)
2	SF 2	1	2	(0.5%)
3	SF 3	1	2.5	(0.5%)
4	SF 4	2	1.5	(0.5%)
5	SF 5	2	2	(0.5%)
6	SF 6	2	2.5	(0.5%)
7	SF 7	3	1.5	(0.5%)
8	SF 8	3	2	(0.5%)
9	SF 9	3	2.5	(0.5%)

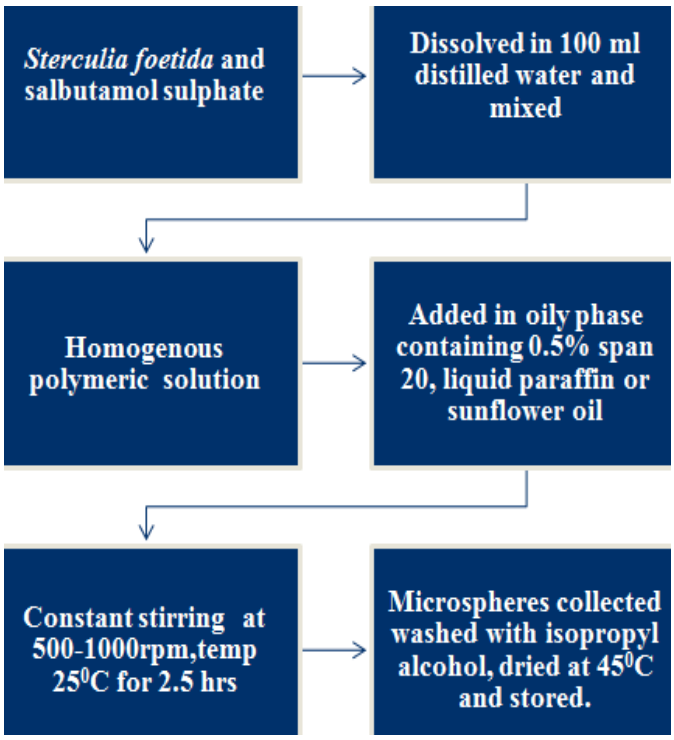

FIG. 1: SCHEMATIC REPRESENTATION OF PREPARATION SALBUTAMOL SULPHATE MICROSPHERES BY SOLVENT EVAPORATION TECHNIQUE

Flow Properties: The flow properties of drug-loaded microspheres were investigated by measuring the angle of repose using fixed base cone method. The bulk and tapped densities were also measured in a 10ml graduated measuring cylinder as a measure of packability of the microspheres.

The angle of repose (θ) was determined by the formula, $\theta = \tan^{-1}(h/r)$; h=cone height of microbeads; r = radius of the circular base [10]. Each experiment was carried out in triplicate.

Particle size analysis [7]: The microsphere size distribution was determined by the method using a calibrated stage micrometer (µm). Different sizes in a batch were determined by MOTIC PLUS – 2.0 ml instrument. The average sizes of the microspheres were calculated.

Percentage yield: The dried microspheres of each batch are weighed separately and percentage yield is calculated by using following equation:

Percentage Yield= $\frac{\text{Practical Weight}}{\text{Theoretical Weight}} \times 100$

Drug Content: 50mg of mucoadhesive microspheres were weighed and powdered. This was dissolved in phosphate buffer (6.8 pH) in 100 ml volumetric flask and made up to volume. The solution was shaken occasionally for 1h and filtered. From this, 1ml of solution was diluted upto 100 ml with pH 6.8 buffer solution in 100 ml volumetric flask. The drug content was analyzed by measuring absorbance in a UV spectrophotometer at 270 nm using pH 6.8 phosphate buffer as blank. The studies were carried out in triplicate. Drug content is calculated by the formula:

Drug Loading (%) = $\frac{W_d}{W_m} \times 100$

Where, W_d is the weight of drug, W_m the weight of the microspheres.

Microencapsulation efficiency: 100mg of mucoadhesive microspheres were accurately weighed. They were powdered and extracted with 100 ml of methanol. Further, it was serially diluted with pH 6.8 phosphate buffer solution. The resulting solution was analyzed for salbutamol sulphate drug content by measuring absorbance in a UV spectrophotometer at 270 nm using pH 6.8 phosphate buffer as blank. The studies were carried out in triplicate. Encapsulation efficiency (%) was calculated using the formula;

Encapsulation Efficiency=

$\frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \times 100$

Swelling Index: Swelling index is determined by measuring the extent of swelling of microspheres in a phosphate buffer pH 6.8 . To ensure the complete equilibrium, exactly weighed 100 mg of microspheres are allowed to swell in buffer for 34 hrs. The excess surface adhered liquid drops are removed by blotting and the swollen microspheres are weighed by using microbalance. The Hydrogel microspheres then dried in an oven at 60° for 5 hrs until there is no change in the dried mass of sample. The swelling index of the microspheres is calculated by using the formula;

Swelling Index=

$\frac{\text{Mass of Swollen MS - Mass of Dry MS}}{\text{Mass of Dried MS}} \times 100$

Percentage of moisture loss: The salbutamol sulphate loaded microspheres of different polymers were evaluated for percentage of moisture loss which sharing an idea about its hydrophilic nature. The microspheres weighed initially and kept in desiccators containing calcium chloride at 37°C for 24 hours. When no further change in weight of sample was observed, the final weight was noted down.

$$\% \text{ Moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

***In-vitro* mucoadhesion [8]:** The mucoadhesive property of microspheres was evaluated by an *in vitro* adhesion testing method known as wash off method. Freshly excised piece of intestinal mucosa (2 x 2 cm) from albino rat were mounted onto glass slides (3 x 1 inch) with cyanoacrylate glue.

Two glass slides were connected with a suitable support, about 50 microspheres were spread on to each wet rinsed tissue specimen and immediately thereafter the support was hung onto the arm of a USP tablet disintegrating test machine.

When the disintegrating test machine was operated, the tissue specimen was given slowly, regular up and down moment in the test fluid (500 ml pH 6.8 phosphate buffer) maintained at 37º C. At the end of 30 min, 1h, and hourly intervals upto 6h, the number of microspheres adhering to tissue were counted.

$$\% \text{ Mucoadhesion} = \frac{\text{Wt of adhered microspheres}}{\text{Weight of applied microspheres}} \times 100$$

***In-vitro* drug release studies [9]:** The release of Salbutamol sulphate from mucoadhesive microspheres was investigated in pH 6.8 phosphate buffer solution as a dissolution medium (900 ml) using USP type I apparatus. A sample of microspheres equivalent to 50 mg of salbutamol sulphate were taken in the muslin cloth tied on to the paddle of apparatus. A speed of 50

rpm and temperature of 37±0.5°C was maintained throughout the experiment. At fixed intervals, aliquots (5 ml) was withdrawn and replaced with fresh dissolution media.

The concentration of drug released at different time intervals was then determined by measuring the absorbance using Hitachi U-2000 spectrophotometer at 276 nm against blank. The studies were carried out in triplicate. The *in vitro* dissolution data of oral mucoadhesive microspheres were tabulated and calculated by using dissolution software viz., PCP DISSO V3.0.

***In-vitro drug* release kinetics:** In order to study the exact mechanism of the drug release from microspheres, drug release data was analyzed according to Zero Order, First Order, Higuchi square root, Hixon Crowell, Korsemeyer model. The criterion for selecting the most appropriate model was chosen on the basis of goodness to fit test.

To analyze the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted in to Zero order, First order, Higuchi matrix and Korsemeyer and Peppas model. Using PCP-DISSO – v2 software. Comparing the r^2-values obtained, the best-fit model was selected.

Scanning Electron Microscopy [10]: The particle size, shape and surface morphology of micro-spheres were examined by scanning electron microscopy (SEM). Microspheres were fixed on aluminium studs and coated with gold using a sputter coater SC 502, under Vacuum [0.1 mm Hg]. The microspheres were then analyzed by scanning electron microscopy (SEM) [Model JSM-840 A, Joel. Japan].

Drug – excipients compatibility studies: Drug-Excipients Compatibility were done by Fourier Transform Infrared Spectroscopy (FTIR).

Fourier Transform Infrared Spectroscopy (FTIR): The compatibility between pure drug and polymers were detected by IR spectra obtained on Perkin Elmer 1600 series, (USA). The pellets were prepared on KBr–press. To prepare the pellets, a few mg of the microspheres were ground together in a mortar with about 100 times quantity of KBr. The finely ground powder was introduced into a stainless steel die. The powder was then pressed in the die between polished stainless steel anvils at a pressure of about 10t/in^2. The spectra were recorded over the wave number range of 4000 to 500 cm-1.

Stability studies [11]: Selected microspheres (formulation code SF 2, SF 6, SF 8, SF 9) were wrapped in aluminium foil and packed in glass vials. These formulations were then kept in an incubator maintained at 40±0.50 C and 75±5% RH for 60 days. Changes in the particle size , drug content, drug release and appearance of these stored microspheres were investigated at regular intervals (0 days, 15 days , 30 days, 45 days, 60 days).

RESULTS AND DISCUSSION:

Evaluation of Mucoadhesive Microspheres: All the evaluation parameters were performed with all the 18 batches. But from the results of micromeritic properties, swelling studies, drug content, encapsulation efficiency, % yield and particle size of microsphere batches prepared in sunflower oil showed better than of the microsphere batches of liquid paraffin. Thus, the batches of microspheres prepared from sunflower oil were considered for further studies. Further from *in vitro* mucoadhesion and release studies four batches were optimized S2, S6, S8 and S9.

The Salbutamol sulphate (SS) microspheres were prepared by W/O Emulsion solvent evaporation technique by using natural polymer i.e. *Sterculia foetida* gum (SFG). Total 18 formulations were prepared. 9 formulations were prepared from sunflower oil and 9 formulations were prepared from liquid paraffin oil. The prepared formulations were then evaluated for different properties.

Micromeritic properties: It was noticed that from the two different oil batches, sunflower oil batches showed better results compared to liquid paraffin batches. The microspheres prepared from sunflower oil were easily washed compared to liquid paraffin. They also showed excellent flowability this may be due to less viscosity of sunflower oil than liquid paraffin (**table 3**).

TABLE 3: MICROMERITIC PROPERTIES OF MICROSPHERES FROM SUNFLOWER OIL

SUNFLOWER OIL (Mean ± S.D ; n= 3)					
Batch	**Angle of repose (Ɵ)**	**Bulk density (g/ml)**	**Tapped density(g/ml)**	**% Carr's index**	**Hausner's ratio**
S1	22.5± 0.21	0.325± 0.007	0.38± 0.01	14.4± 0.42	1.16± 0.02
S2	22.9± 0.07	0.28± 0.0013	0.32± 0.03	12.5± 0.35	1.14± 0.06
S3	20.65± 0.03	0.267± 0.0014	0.307± 0.06	13.0± 1.41	1.14± 0.07
S4	21.0± 0.70	0.291± 0.002	0.336± 0.002	13.39± 1.13	1.15± 0.07
S5	24.4± 0.14	0.284± 0.002	0.331± 0.002	14.1± 0.565	1.16± 0.05
S6	21.5± 0.14	0.304± 0.002	0.334± 0.004	8.9± 0.070	1.09± 0.04
S7	23.6± 0.07	0.286± 0.001	0.312± 0.009	8.3± 0.424	1.09± 0.12
S8	22.2± 0.35	0.34± 0.011	0.396± 0.01	14.14± 0.46	1.16± 0.08
S9	20.74± 0.18	0.311± 0.002	0.37± 0.02	15.9± 0.28	1.18± 0.07

Particle size analysis : It was noticed that the particle size of microspheres increases with the increased concentration of *Sterculia foetida* and this may be due to high viscosity of *Sterculia foetida* gum which increases the droplet size and results in increase particle size (**fig. 2, table 4**).

Percentage yield: It was noticed that % yield of microspheres prepared from sunflower oil has the maximum yield compared to batches prepared from liquid paraffin (**table 5**).

Drug content: The drug content in microspheres using sunflower oil as oil phase was more than that with liquid paraffin batches S7 showed highest drug content (table 5).

Microencapsulation efficiency: Micro-encapsulation efficiency was more with sunflower oil as oil phase showed good microencapsulation efficiency with maximum microencapsulation efficiency of 96.8% with batch S9. The entrapment efficiency is increased with the lower concentration of *Sterculia foetida* polymer (table 5).

Swelling property : The swelling indices increase with the increase in concentration of *Sterculia foetida* gum. It was noticed that the swelling indices of the microspheres prepared from sunflower oil were high as compared to microspheres prepared from the liquid paraffin (**fig. 3**).

% Moisture loss: The % moisture loss was determined for all the formulations prepared from sunflower oil and liquid paraffin. It was noticed that the microspheres prepared from sunflower oil show minimum Percent moisture loss as compared to Microspheres prepared from liquid paraffin (**fig. 4**)

***In-vitro* mucoadhesion test:** The no. of micro-spheres adhering to the tissue were calculated after 2hr, 4hr, 6hr, 8hr. After determination it was found that batch S9 showed highest percent 78% mucoadhesion than other batches. Three batches showed comparatively higher muco-adhesion in the following order **S6<S8<S9** (**fig. 5**).

***In-vitro* release studies**: The maximum *in-vitro* drug release was found to be 99.77% for formulation S9 at 12th hour. Formulation S6, S8 showed maximum release of 95.8%, 97.07% respectively at 12th hour. The release data were analyzed on the basis of best fitting models. The release rates k and n of each model were calculated by linear regression analysis. Coefficients of correlation (r^2) were used to evaluate the accuracy of the fit (**table 6, fig. 6**).

FTIR Studies: FTIR Spectral analysis was performed to study the drug polymer interaction.It was concluded that there were no changes in the peak shape and no shift of peaks. Thus, there is no interaction between drug polymer. So they are compatible with each other (**fig. 7-12**).

Scanning electron microscopy: SEM of the selected formulation was performed. All the selected microspheres loaded with salbutamol sulphate were smooth, almost spherical, and uniform.(fig 13-16)

Accelerated stability studies: Accelerated stability study data of the medicated microspheres are shown in **table 7**. At the initial level and at the final level of the accelerated stability study, the tested microspheres showed almost similar particle size, drug content and drug release were observed. No color changes or unexpected change were observed. All the optimized batches were

found stable after 2 months without much variation in particle size, drug content, drug release.

Micromeritic properties of prepared Mucoadhesive Microspheres:

Physical Characterization of Prepared Microspheres

TABLE 4: PARTICLE SIZE AND SHAPE OF MICROSPHERES PREPARED FROM SUNFLOWER OIL

SUNFLOWER OIL (Mean ± S.D ; n= 3)		
Formulation code	**Particle size (radius in (µm)**	**Shape**
S 1	16.03 ± 0.28	Spherical
S 2	10.4 ± 0.28	Spherical
S 3	12.5 ± 0.35	Spherical
S 4	18.2 ± 0.84	Spherical
S 5	14.9 ± 1.41	Spherical
S 6	20.9 ± 0.31	Spherical
S 7	20.3 ± 1.13	Spherical
S 8	21.4 ± 0.21	Spherical
S 9	35.3 ± 0.14	Spherical

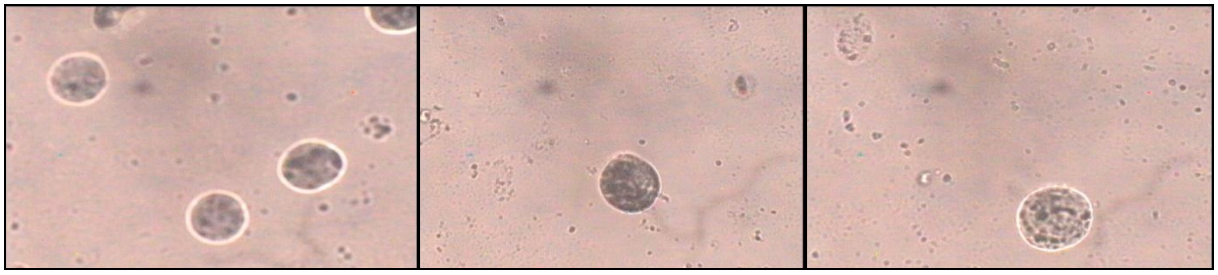

FIG. 2: PARTICLE SIZE ANALYSIS OF SALBUTAMOL SULPHATE WITH STERCULIA FOETIDA GUM USING LIQUID PARAFFIN AND SUNFLOWER OIL BATCHES

Percentage yield, Drug Content and Percent Drug Entrapment:

TABLE 5: PERCENTAGE YIELD, DRUG CONTENT AND PERCENT DRUG ENTRAPMENT OF MICROSPHERES FROM SUNFLOWER OIL (Mean ± S.D., n=3)

Sr. No	Formulation Code	Percent Yield (%)	Drug Content (%)	Entrapment Efficiency (%)
1	SF 1	56.48± 0.10	40.01± 0.7	84.5± 0.7
2	SF 2	46.53± 0.12	33.3± 0.9	87.16± 0.4
3	SF 3	84.51± 0.06	28.56± 0.6	80.74± 0.32
4	SF 4	64.22± 0.15	56.9± 1.13	79.5± 0.56
5	SF 5	32.4± 0.35	50± 1.14	81.36± 0.67
6	SF 6	70.57± 0.16	44.3± 1.13	90.89± 0.84
7	SF 7	41.68± 0.07	66.6± 0.49	88.4± 1.06
8	SF 8	48.08± 0.43	59.9± 0.77	92.9± 0.63
9	SF 9	52.14± 0.46	54.3± 0.98	96.8± 0.63

Percent Moisture Loss and Swelling Index:

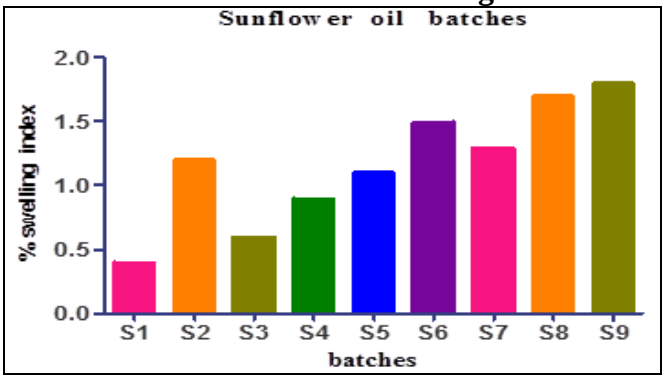

FIG. 3: % SWELLING OF SUNFLOWER OIL BATCHES

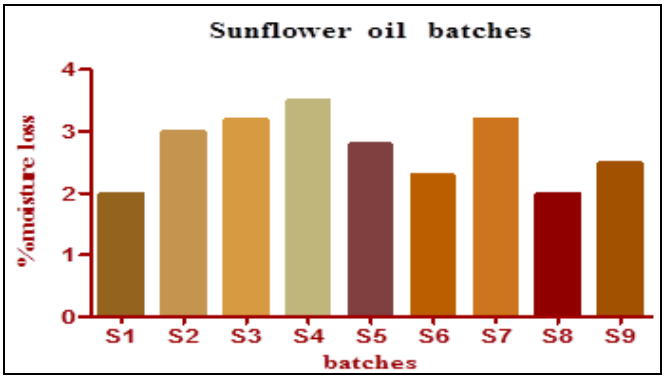

FIG. 4: % MOISTURE LOSS OF SUNFLOWER OIL BATCHES

In-vitro Mucoadhesion test:

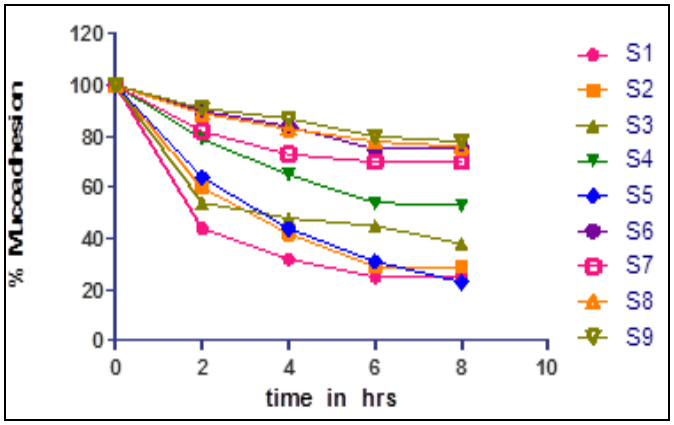

FIG. 5: MUCOADHESION BEHAVIOR OF MUCOADHESIVE MICROSPHERES FORMULATIONS PREPARED IN SUNFLOWER OIL pH 6.8

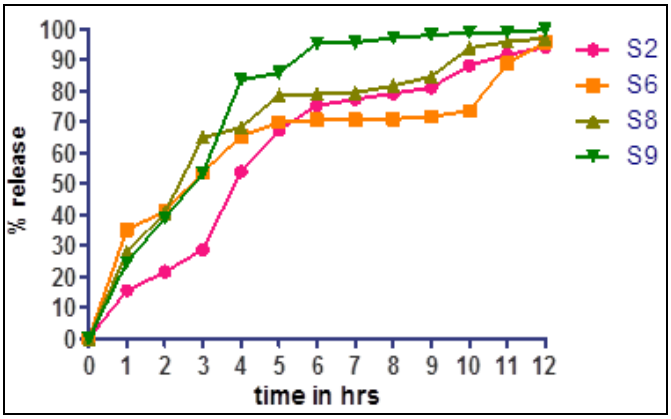

FIG. 6: *IN-VITRO* DRUG RELEASE OF SALBUTAMOL SULPHATE FROM S2, S6, S8, S9 BATCHES

In-vitro drug release studies:

TABLE 6: *IN VITRO* DRUG RELEASE DATA OF SALBUTAMOL SULPHATE MICROSPHERES WITH *STERCULIA FOETIDA* (Mean ± S.D., n=3)

	Cumulative % drug release (Mean ± S.D ; n= 3)			
Time in hrs	**S2**	**S6**	**S8**	**S9**
0	0	0	0	0
1	25.184±0.76	35.191±1.54	27.944±0.03	24.564± 0.30
2	35.109±1.40	41.096±0.63	40.599±0.28	39.067± 0.65
3	44.922±1.21	53.605±0.27	64.939±0.04	53.407± 0.41
4	60.050±0.90	65.397±0.96	68.193±0.57	83.507± 0.34
5	66.908±0.23	69.796±1.26	78.604±0.28	85.914± 0.06
6	67.423±1.34	70.592±0.28	79.052±0.67	95.445± 0.39
7	67.927±0.14	70.782±1.96	79.490±1.06	95.611± 0.86
8	69.305±0.67	70.964±0.73	81.686±0.22	97.184± 0.57
9	69.784±1.03	71.727±0.19	84.730±0.19	98.029± 0.47
10	84.238±0.53	73.640±0.25	93.853±0.10	98.858± 1.31
11	84.614±1.68	88.852±0.10	95.911±0.77	98.975± 0.15
12	86.708±0.20	95.816±0.13	97.074±1.36	99.775± 0.01

Drug-polymer interaction studies:

FTIR Studies: The FTIR spectrum of Salbutamol sulphate and *Sterculia foetida* gum alone and the Optimized batches of Microspheres were presented in figures:

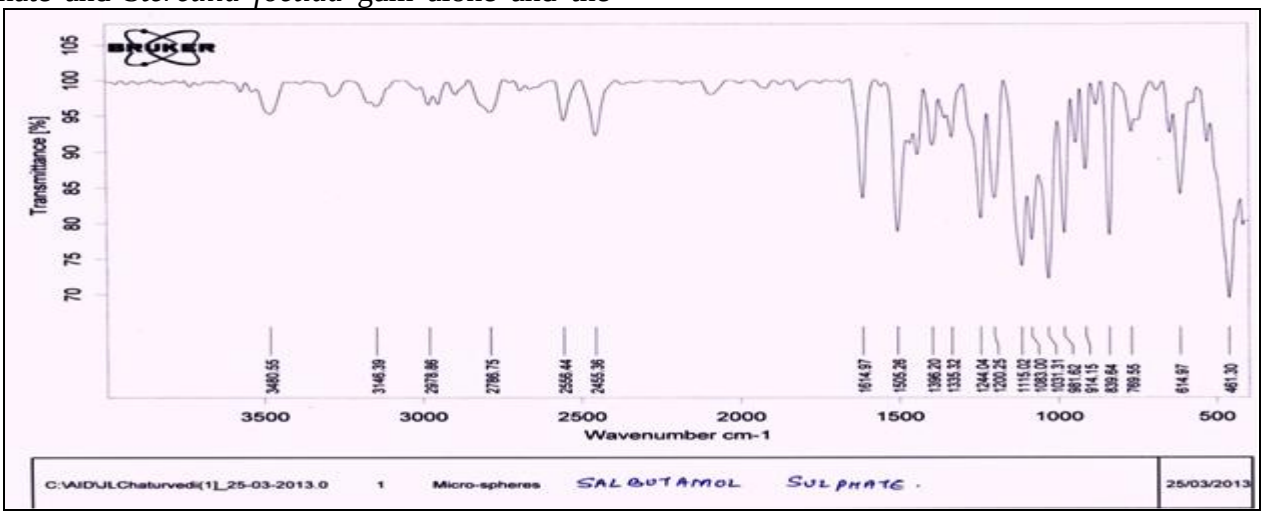

FIG. 7: INFRARED SPECTRUM OF SALBUTAMOL SULPHATE

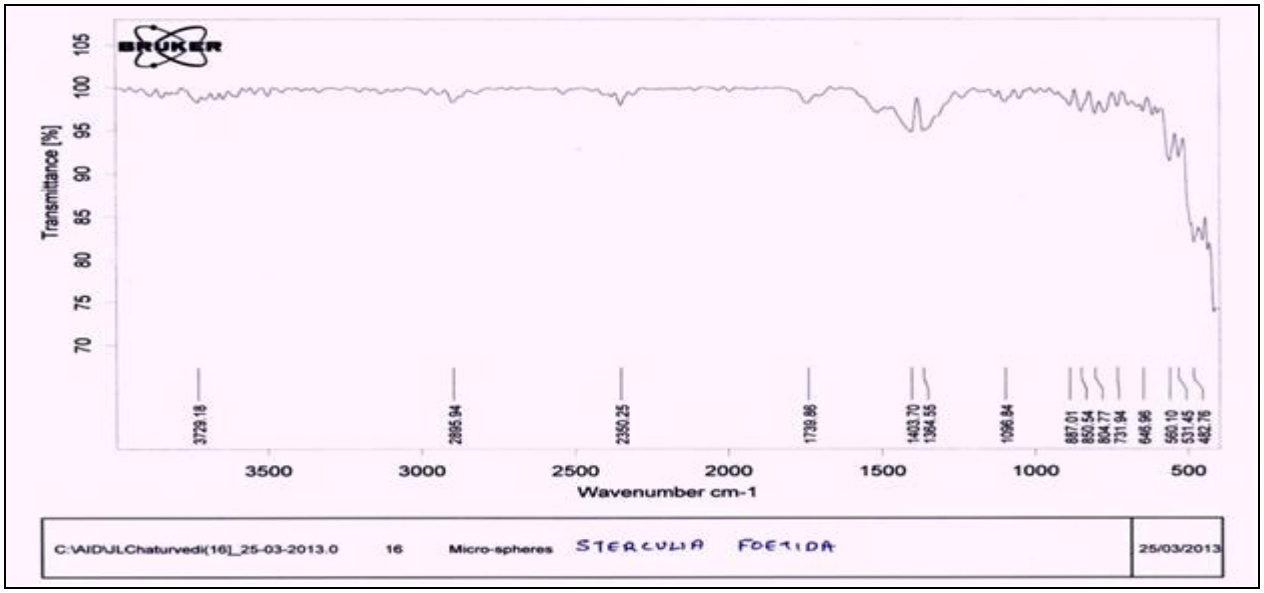

FIG. 8: INFRARED SPECTRUM OF STERCULIA FOETIDA GUM

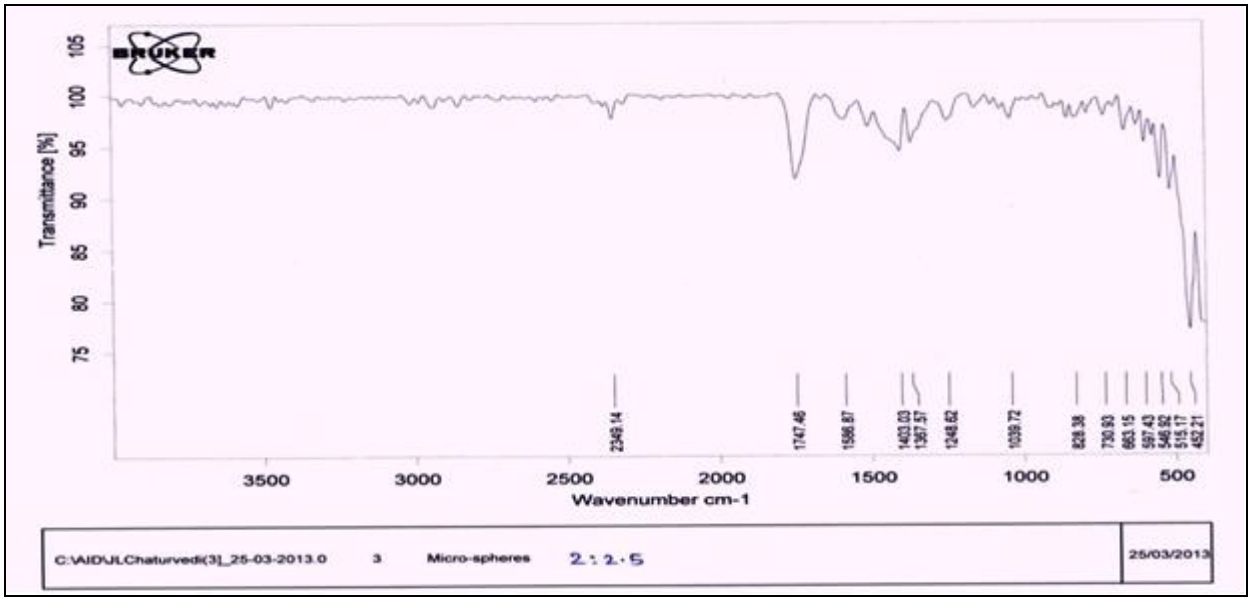

FIG. 9: INFRARED SPECTRUM OF S6 BATCH

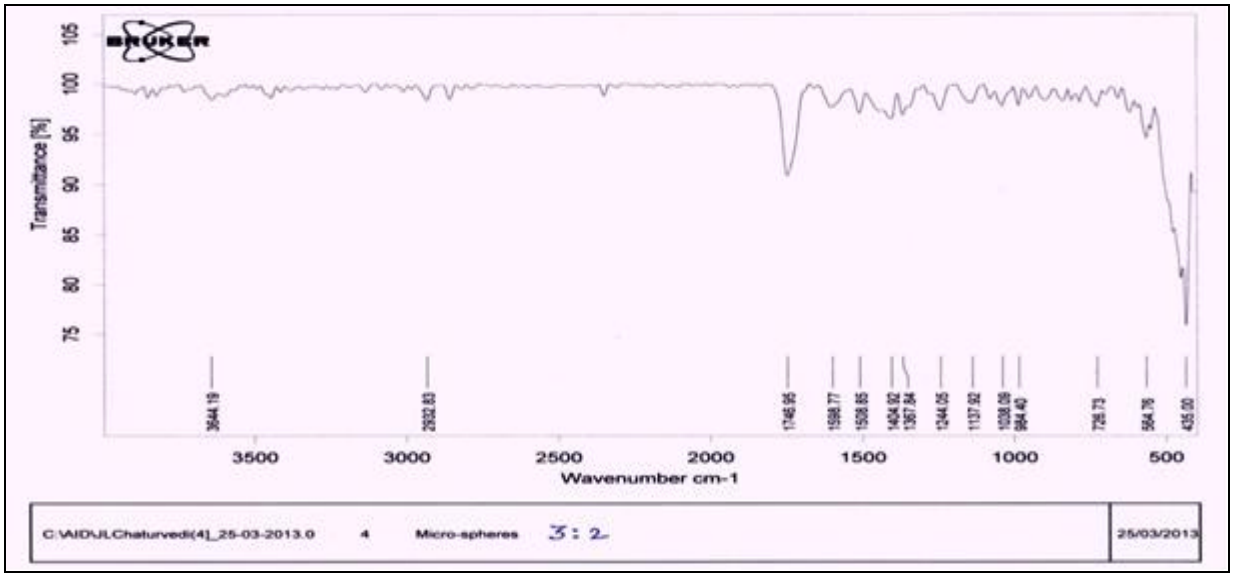

FIG. 10: INFRARED SPECTRUM OF S8 BATCH

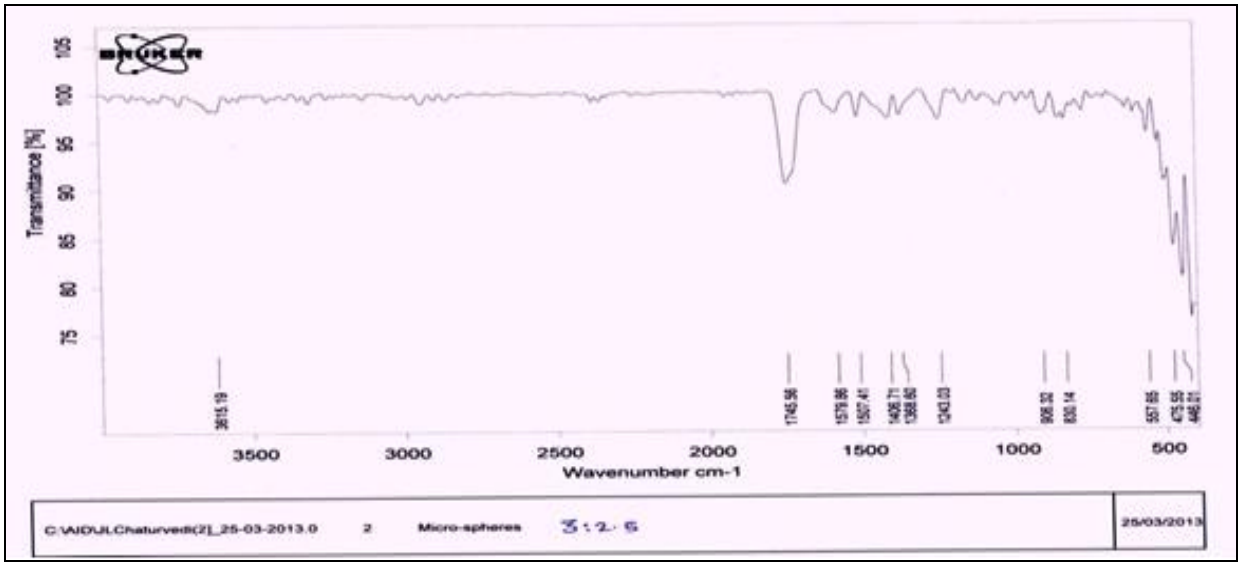

FIG. 11: INFRARED SPECTRUM OF S9 BATCH

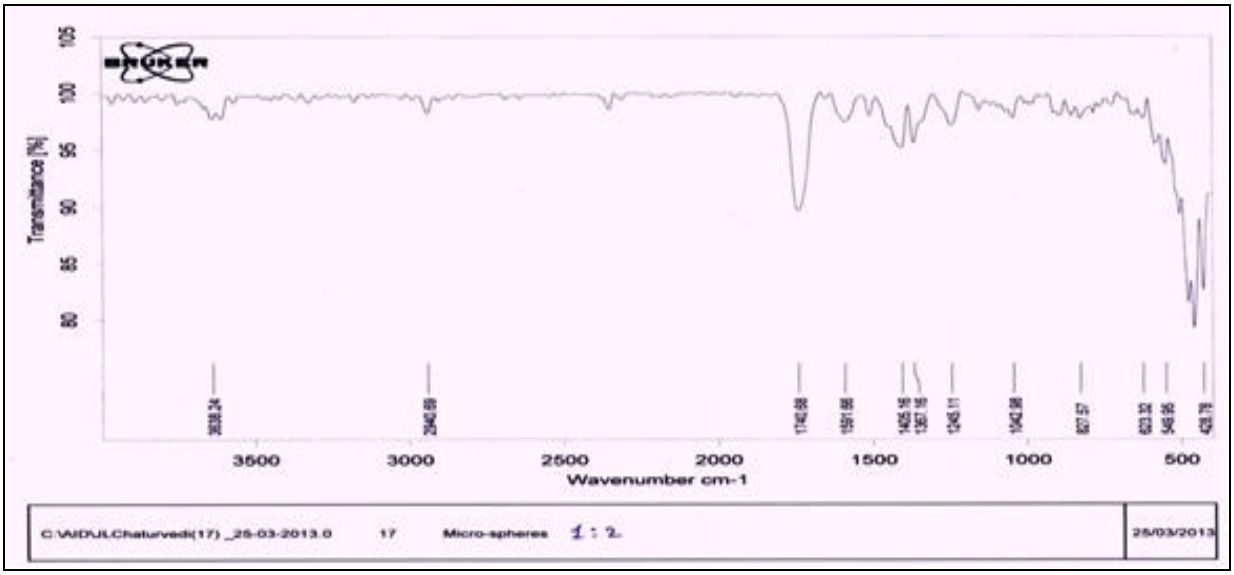

FIG. 12: INFRARED SPECTRUM OF S2 BATCH

Scanning Electron Microscopy:

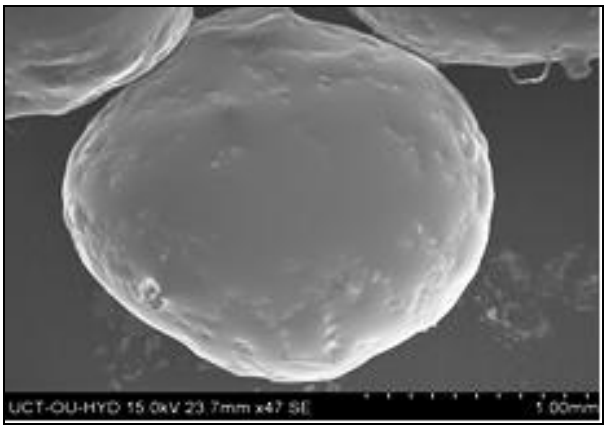

FIG. 13: S2 BATCH

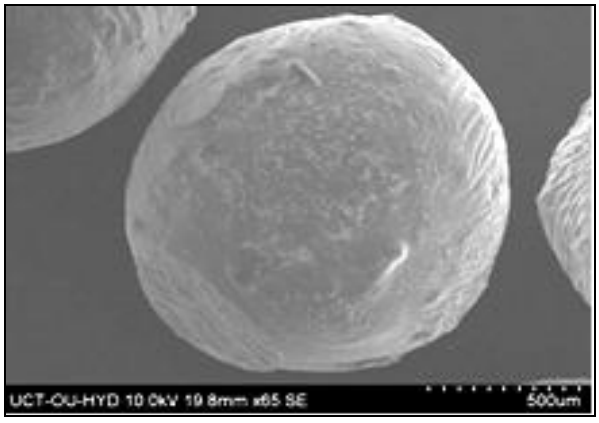

FIG. 14: S6 BATCH

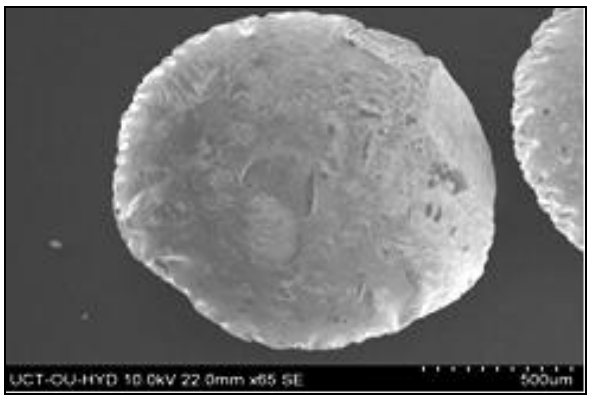

FIG. 15: S8 BATCH

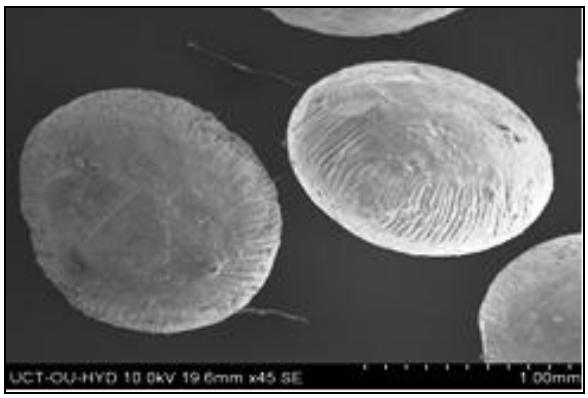

FIG. 16: S9 BATCH

Accelerated Stability Studies:

TABLE 7: PHYSICAL STABILITY CHARACTERISTICS OF SELECTED SALBUTAMOL SULPHATE MICROSPHERES: (Mean ± S.D; n = 3) Condition : room temp: 40° C , relative humidity:75%

Evaluation parameter	Formulation code	Sampling Intervals in Days				
		0	15	30	45	60
Particle size (µm)	S2	10.4±0.14	10.1±1.41	9.8±0.28	9.4±0.14	9.3±0.02
	S6	20.9±0.21	20.2±0.84	19.9±0.21	19.3±0.12	19.1±0.41
	S8	21.4±1.13	21.1±0.35	20.7±0.70	20.2±0.21	20.1±0.35
	S9	35.3±0.31	35.2±0.28	35.1±0.28	34.9±0.19	34.8±0.21
Drug content (mg)	S2	33.3±0.7	33.0±0.77	32.5±0.68	31.8±1.54	31.6±0.03
	S6	44.3±0.9	44.1±0.84	43.9±0.30	43.5±0.27	43.2±0.28
	S8	59.9±0.6	59.5±1.44	59.0±1.34	58.7±1.26	58.5±0.57
	S9	54.3±1.13	54.1±0.84	53.9±0.98	53.5±0.28	53.2±0.28
Drug release (%)	S2	86.71±1.14	85.7±0.42	84.6±0.29	84.1±0.73	84.0±0.67
	S6	95.8±1.13	94.7±0.77	93.5±0.68	93.0±0.19	92.9±0.19
	S8	97.07±0.77	96.1±0.91	95.08±0.07	94.9±0.10	94.1±0.77
	S9	99.77±0.49	98.7±0.63	98.1±0.29	97.8±0.13	97.6±0.15

CONCLUSION: From the above experimental results, it can be concluded that:

- Oral controlled release of Salbutamol sulphate can be achieved by solvent evaporation technique using *Sterculia foetida* as a polymer.
- The IR spectra's revealed that, there was no interaction between polymer and drug. The entire polymer used was compatible with the drug.
- Prepared microspheres exhibited Korsemeyer-Peppas kinetics/Higuchi model and the release profile was by Fickian and Anomalous
- From the study, it is evident that a promising controlled release microparticulate drug delivery of salbutamol sulphate can be developed. Further, *in-vivo* investigation is required to establish efficacy of these formulations.
- The study also indicated that the amount of drug release decreases with an increase in the polymer concentration .
- Finally, it can be concluded that the micro-spheres of salbutamol sulphate can offer the following potential advantages:

  1. Reduced frequency of administration
  2. Increased therapeutic response
  3. Improve patient compliance
  4. Improved flow and packing property.

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