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FORMULATION AND EVALUATION OF SALBUTAMOL SULPHATE NANOPARTICLES

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ABSTRACT

The aim of the study was to prepare Salbutamol Sulphate using nanoprecipitation method using different drug and polymer ratio. FT-IR studies revealed that there was no chemical interaction between the drug and polymer. The average particle size of the optimized formulation was found to be 365nm. The *in-vitro* release behaviour from all the Salbutamol Sulphate loaded nanoparticles was found to be zero-order and produced a sustained release over a period of 12 hours with better entrapment efficiency.

KEYWORDS

Salbutamol Sulphate, Nanoprecipitation technique, Entrapment efficiency and *In vitro* release study.

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INTRODUCTION

Novel drug delivery system aims to deliver drug at a rate directed by the needs of the body during the period of treatment and channel the active entity to the site of action. The method by which the drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in

tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs were generated. These new strategies, often called drug delivery systems (DDS), are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology.

Nanoparticles represent a very promising drug delivery system of sustained and targeted drug release. Nanoparticles are solid colloidal particles ranging in size from 1 to 1000nm. They consist of macromolecular materials and can be used therapeutically, for example as adjuvant in vaccines or drug carries, in which the drug is dissolved, entrapped or encapsulated. Speiser and co workers in the late 1960"s and early 1970"s first developed in significance of using nanoparticles as a vehicle for drug delivery when cross linked polyacrylamide nanoparticles were produced by the polymerization of acrylamide and N,N 1-methylene bis acrylamide afte secondary solubilization in an organic solvent such as hexane. The active ingredients, drugs, antigens were incorporated into the solubilized aqueous phase[1-5].

MATERIAL AND METHODS

Salbutamol Sulphate, Sodium lauryl sulphate from Sisco research laboratory pvt.ltd Mumbai, Poly ethylene glycol from Moly chemical Mumbai, acetone from Nice chemical pvt. Ltd, Kochi, Span 80 from Loba chemical pvt.ltd, Mumbai. All the chemicals used were analytical grade.

Formulation of Salbutamol Sulphate Nanoparticles

Nanoprecipitation method is also called solvent displacement method (Table No.1). It involves the precipitation of performed polymer from an organic solution and the diffusion of the organic solvent in aqueous medium. The polymer Poly ethylene glycol (6000), Drug Salbutamol Sulphate dissolved in solvent acetone. This phase is injected to a stirred aqueous solution containing stabilizer as a surfactant, which is placed in probe sonicator for 15 minutes. The polymer deposition on the interphase between the water and organic solvent caused by fast diffusion of solvent, leads to instantaneous formation of Salbutamol Sulphate nanoparticles[1-5].

RESEARCH ENVISAGED[6-15]

Particle size analysis

Average particle size and poly dispersibility index of formulation were determined by Malvern Zetasizer ZS (Nano series ZS 90 UK) using water as dispersion medium. The sample was scanned 100 times for determination of particle size.

IR Studies

IR by KBr pellet method was carried out on pure substances and physical mixtures.

The spectrum of physical mixture was compared with the original spectra to determine any possible molecular interactions between the drug and polymer. FTIR analysis measures the selective absorption of light by the vibration mode of specific chemical bonds in the sample. The observation of vibration spectrum of encapsulated drug evaluates the kind of interaction occurring between the drug and polymer.

Entrapment efficiency

Entrapment efficiency indicated that the amount of drug encapsulated in the formulation .the method of choice of separation is the drug content determination is separation of free drug by ultra centrifugation, followed by quantitative analysis from the formulation. The samples were centrifuged by using ultracentrifuge at 17640 rpm for 40 min.

$$\text{Entrapment efficiency} = \frac{\text{Amount of drug encapsulated in the formulation}}{\text{Total amount of drug in the formulation}} \times 100$$

In vitro release study for Niosomal formulations and analysis by UV method[16-18]

Niosomal preparation was taken in dialysis membrane of 5 cm length and suitably suspended in beaker containing 200ml of diffusion medium(Phosphate buffer saline pH 7.4) The medium was maintained at a temperature of 37 ± 0.5^0C. It was stirred by means of magnetic stirrer at a constant speed. Sample of 1ml (diffusion medium) was withdrawn at every 1 hour for 24 hours and replaced the diffusion medium. So that the volume of diffusion medium was maintained constant at 200ml. The sample were measured spectrophotometrically at 303nm.

Kinetics of drug release[19-22]

The optimized formulation was subjected to graphical treatment to assess the kinetics of drug release.

Zero order kinetics

Drug dissolution form pharmaceuticals dosage forms that do not disaggregate and release the drug slowly, that assume that the area does not change and no equilibrium conditions are obtained can be represented by the following equation,

$Q_t = Q_0 + k_0 t$

Where Q_t= amount of drug dissolved in time t.

Q_0=initial amount of the drug in the solution and

K_0=Zero order release constant.

RESULTS AND DISCUSSION

Particle size analysis of Salbutamol Sulphate Nanoparticles

Particle size reveals that the Salbutamol Sulphate nanoparticle shows the size range of 365nm.This account for higher entrapment efficiencies. The zeta potential value is -5.73 mV to make the nanoparticle stable one (Figure No.1). The size and shape of the vesicle varies with the concentration of polymer used (Figure No.2).

IR studies

FTIR analysis indicates that there was no interaction. Bands seen in pure drug also recognized in formulation, so above characteristic peaks of drug indicates, there is no significant interactions (Table No.2) (Figure No.3 and 4).

Entrapment efficiency

After the removal of un entrapped drug the entrapment efficiency of all formulation was studied. Various concentration of polymers influences the entrapment efficiency. In $SSNF_1$ the entrapment efficiency is about 85% which indicates the polymer PEG entrapped the drug. When the polymer concentration gets decreased the entrapment efficiency also get decreased as mentioned in the above table. PEG act as a size controlling polymer. Concentration of polymer gets reduced entrapment efficiency also decreases (Table No.3).

***In vitro* drug release study**

Nanosuspension equivalent to 4mg of salbutamol sulphate was taken for *in vitro* release study. In formulation $SSNF_1$ the drug release was about 75% at 12 hours, this less release of drug takes place because of high entrapment efficiency followed by formulation $SSNF_2$.

In formulation $SSNF_3$ the release from the entrapped drug is about 90% this indicates optimum amount of drug released from the formulations in controlled manner compared to other formulation In formulation F_4 and F_5 the drug release is increased with decreasing concentration of PEG and it showed controlled release of drug with optimum PEG concentration due to entrapment nature of PEG (Table No.4) (Figure No.5).

Kinetics of drug release

A plot of cumulative percentage drug release versus time showed linearity in optimized formulation of salbutamol sulphate. The regression value for salbutamol sulphate was 0.9920 Hence it follows Zero order kinetics.

Table No.1: Composition of Salbutamol Sulphate nanoparticles

S.No	Formulation Code	Drug	PEG (6000)	SLS	Span80	Acetone	Water
1	$SSNF_1$	4mg	4mg	2 mg	5mg	2ml	20ml
2	$SSNF_2$	4mg	3 mg	2 mg	5mg	2ml	20ml
3	$SSNF_3$	4mg	2 mg	2 mg	5mg	2ml	20ml
4	$SSNF_4$	4mg	1.5 mg	2 mg	5mg	2ml	20ml
5	$SSNF_5$	4mg	1 mg	2 mg	5mg	2ml	20ml

Table No.2: FTIR Study of Salbutamol Sulphate nanoparticles

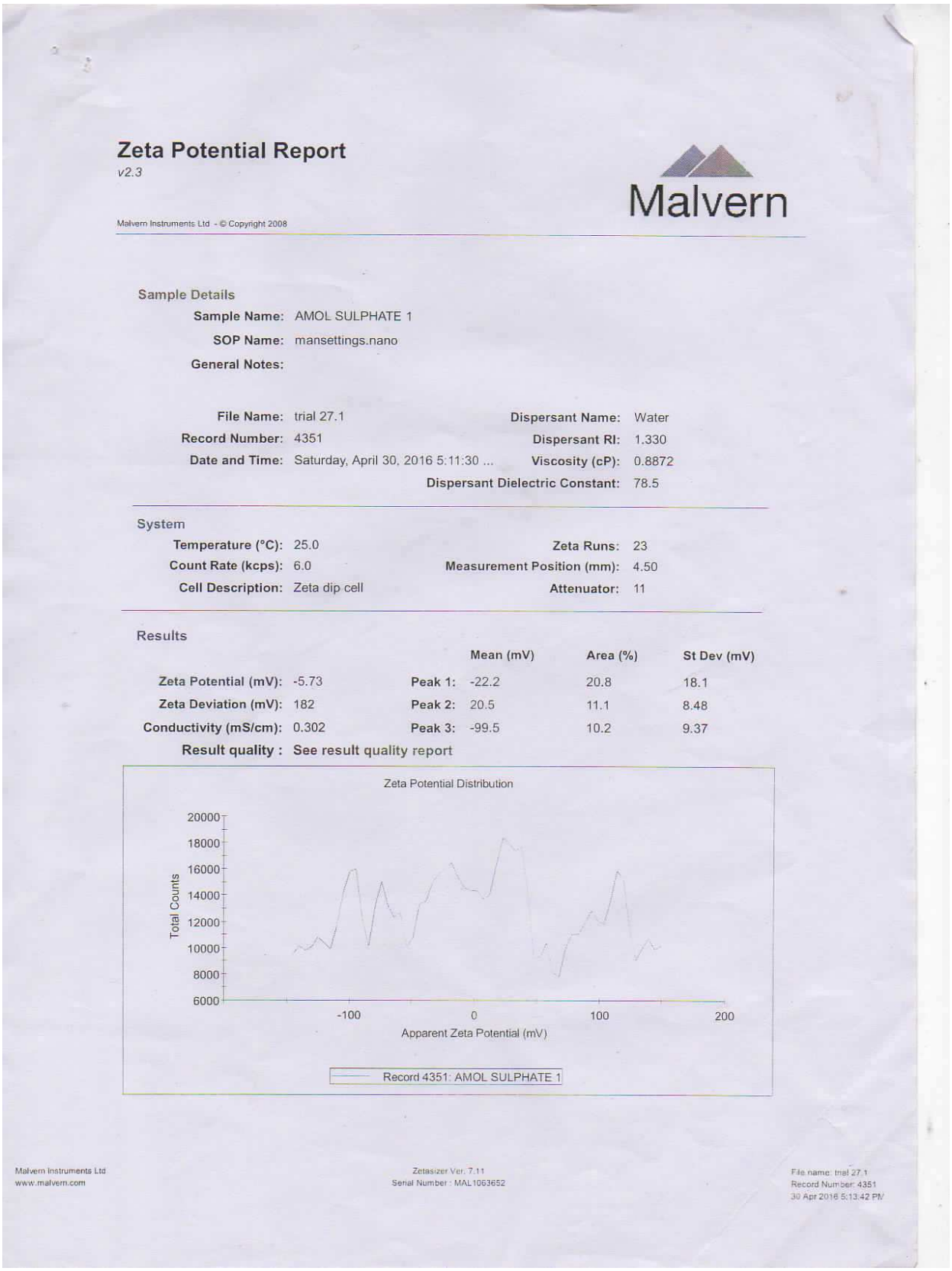
S.No	Frequency(cm^{-1})	Group Assigned
1	3364.91 cm^{-1}	N-H stretching
2	1646.28 cm^{-1}	C=O stretching
3	3330cm^{-1}	O-H stretching

Table No.3: Entrapment efficiency of Salbutamol Sulphate nanoparticles

S.No	FORMULATION	% ENTRAPED DRUG
1	$SSNF_1$	85%
2	$SSNF_2$	82%
3	$SSNF_3$	79%
4	$SSNF_4$	75%
5	$SSNF_5$	72%

Table No.4: Combined *In vitro* release of Salbutamol Sulphate nanoparticles

S.No	$SSNF_1$	$SSNF_2$	$SSNF_3$	$SSNF_4$	$SSNF_5$
1	10%	12.5%	15%	12%	10%
2	12.5%	15%	17.5%	17.5%	15%
3	15%	17.5%	20%	20%	20%
4	17.5%	20%	25%	25%	25%
5	20%	25%	35%	35%	35%
6	35%	35%	45%	45%	45%
7	25%	45%	50%	50%	50%
8	45%	50%	62.5%	62.5%	62.5%
9	50%	62.5%	67.5%	67.5%	67.5%
10	62.5%	67.5%	78%	78%	70%
11	67.5%	70%	80%	80%	78%
12	75%	78%	90%	87.2%	85%



Zeta Potential Report

v2.3

Malvern

Sample Details

Sample Name: AMOL SULPHATE 1
SOP Name: mansettings.nano
General Notes:

File Name: trial 27.1
Record Number: 4351
Date and Time: Saturday, April 30, 2016 5:11:30 ...
Dispersant Name: Water
Dispersant RI: 1.330
Viscosity (cP): 0.8872
Dispersant Dielectric Constant: 78.5

System

Temperature (°C): 25.0
Count Rate (kcps): 6.0
Cell Description: Zeta dip cell
Zeta Runs: 23
Measurement Position (mm): 4.50
Attenuator: 11

Results

		Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV): -5.73	**Peak 1:**	-22.2	20.8	18.1
Zeta Deviation (mV): 182	**Peak 2:**	20.5	11.1	8.48
Conductivity (mS/cm): 0.302	**Peak 3:**	-99.5	10.2	9.37

Result quality : See result quality report

Zeta Potential Distribution

Total Counts: 20000, 18000, 16000, 14000, 12000, 10000, 8000, 6000

-100, 0, 100, 200

Apparent Zeta Potential (mV)

Record 4351: AMOL SULPHATE 1

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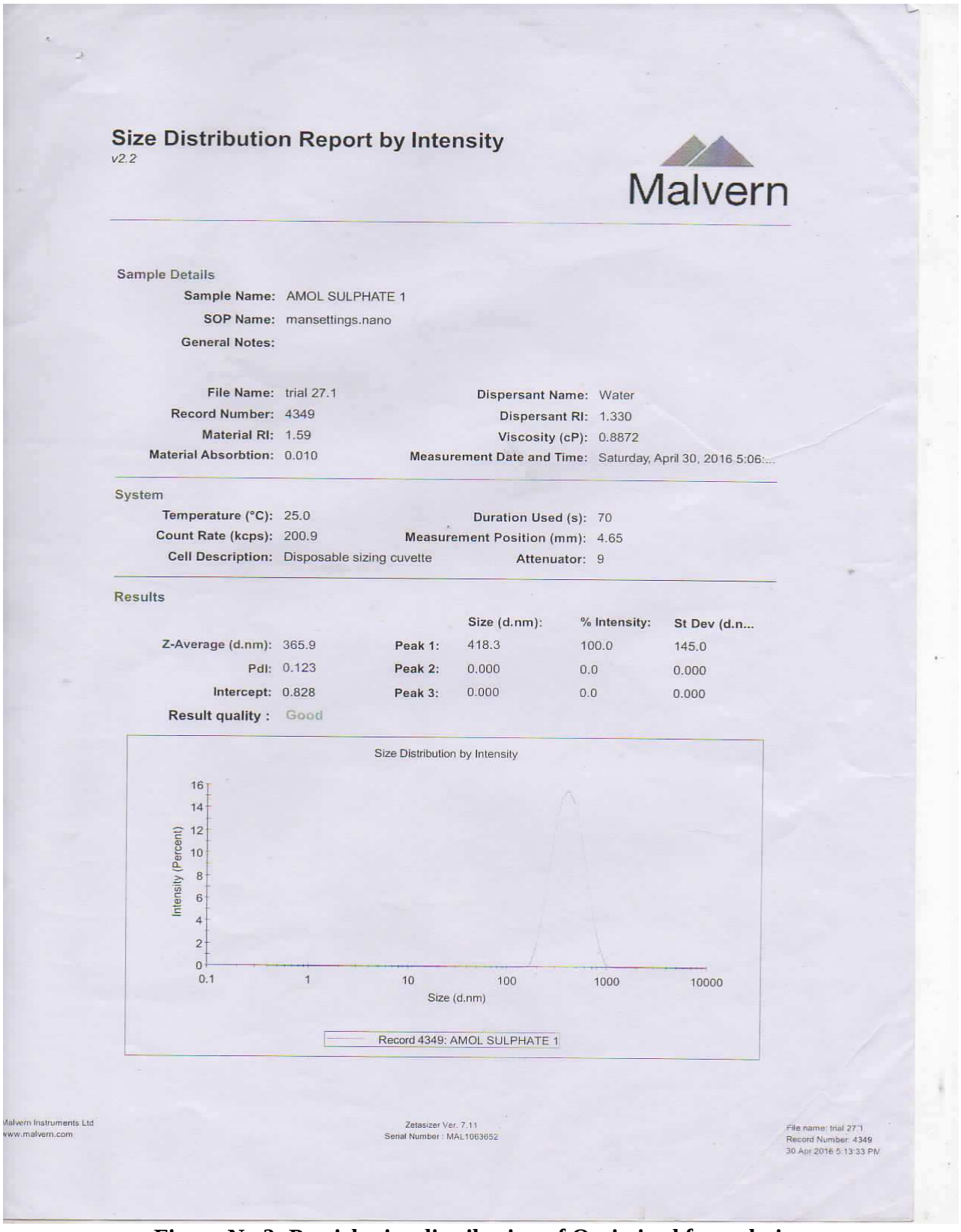
Zetasizer Ver. 7.11
Serial Number : MAL1063652

File name: trial 27.1
Record Number: 4351
30 Apr 2016 5:13:42 PM

Figure No.1: Zeta Potential of Optimized formulation



Size Distribution Report by Intensity

v2.2

Malvern

Sample Details

Sample Name: AMOL SULPHATE 1
SOP Name: mansettings.nano
General Notes:

File Name: trial 27.1
Record Number: 4349
Material RI: 1.59
Material Absorbtion: 0.010
Dispersant Name: Water
Dispersant RI: 1.330
Viscosity (cP): 0.8872
Measurement Date and Time: Saturday, April 30, 2016 5:06:...

System

Temperature (°C): 25.0
Count Rate (kcps): 200.9
Cell Description: Disposable sizing cuvette
Duration Used (s): 70
Measurement Position (mm): 4.65
Attenuator: 9

Results

		Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 365.9	**Peak 1:**	418.3	100.0	145.0
PdI: 0.123	**Peak 2:**	0.000	0.0	0.000
Intercept: 0.828	**Peak 3:**	0.000	0.0	0.000

Result quality : Good

Size Distribution by Intensity

Intensity (Percent)

16
14
12
10
8
6
4
2
0

0.1 1 10 100 1000 10000

Size (d.nm)

Record 4349: AMOL SULPHATE 1

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Zetasizer Ver. 7.11
Serial Number : MAL1063652

File name: trial 27.1
Record Number: 4349
30 Apr 2016 5:13:33 PM

Figure No.2: Particle size distribution of Optimized formulation

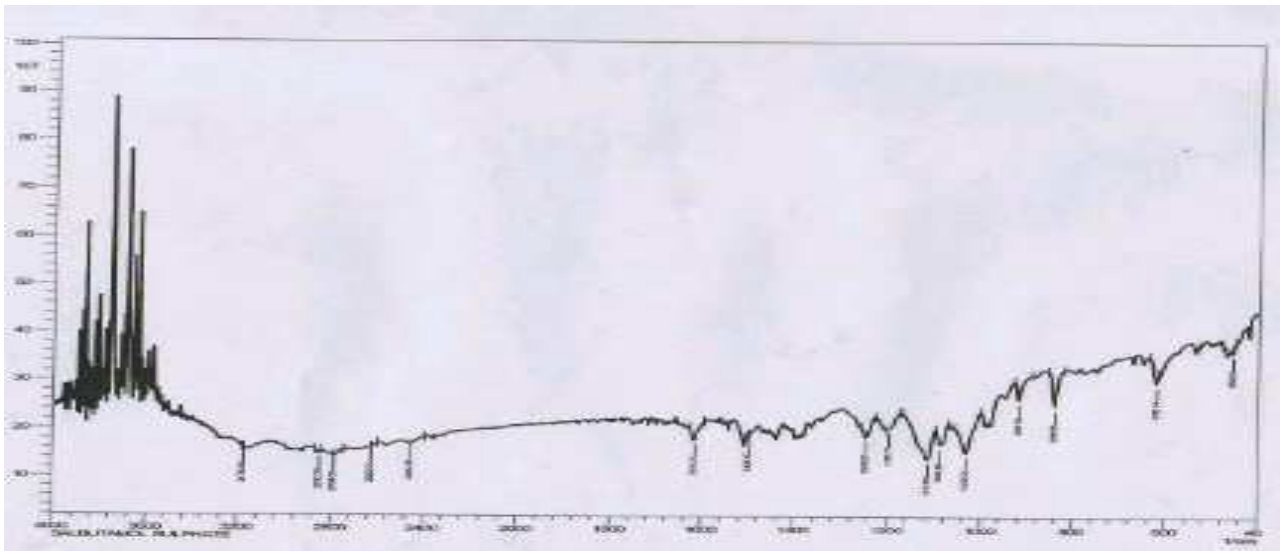

Figure No.3: FTIR of Salbutamol Sulphate

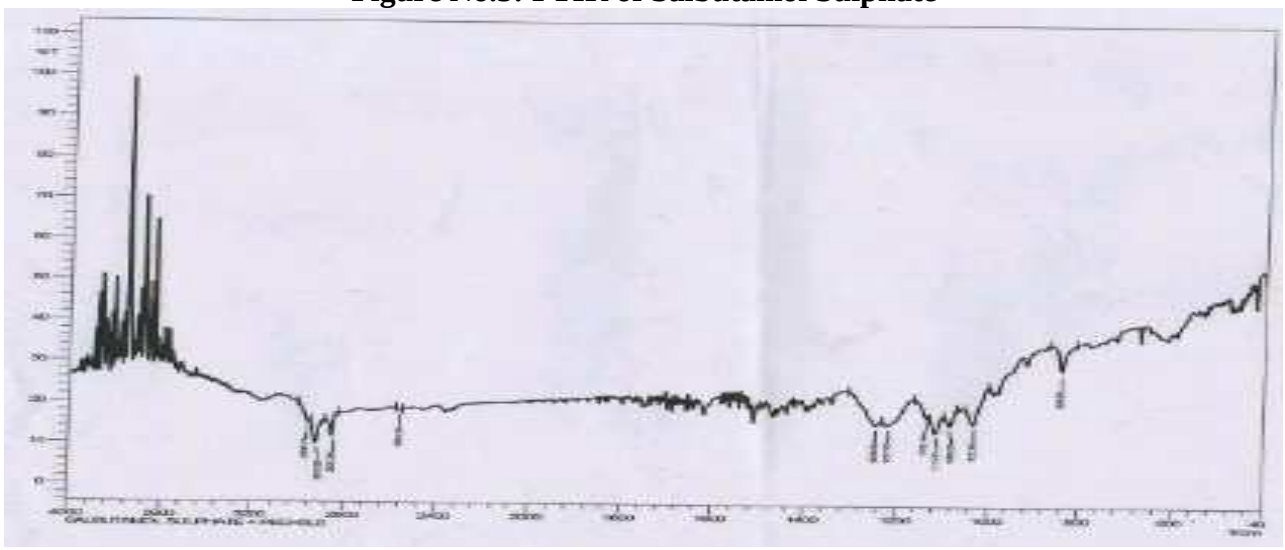

Figure No.4: FTIR of Salbutamol Sulphate and Excipients

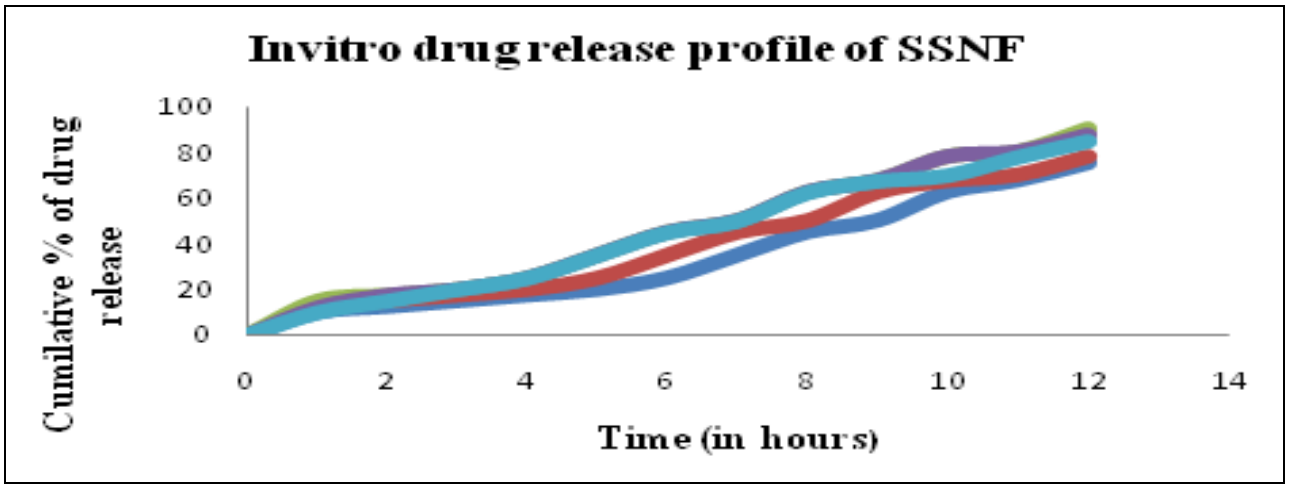

Figure No.5: Combined *In vitro* drug release of Salbutamol Sulphate nanoparticles

CONCLUSION

The aim of present study is to develop formulation of Salbutamol Sulphate nanoparticles. In the preliminary screening, from the FT IR spectra, it was observed that similar functional groups appear for the drug and the formulation. Hence it shows that there was no chemical interaction between drug and polymer used. The formulations $SSNF_1$, $SSNF_2$, $SSNF_3$, $SSNF_4$, $SSNF_5$ prepared by nanosuspension method. $SSNF_3$ Selected as an optimized formulation, because of better entrapment efficiency and *in vitro* drug release of about 90% in 12hours. Particle size study reveals that size of nanoparticle is 365nm, this account for better entrapment efficiency. It follows zero order kinetics release.

Hence it can be concluded that Salbutamol Sulphate can be prepared in the form of nanoparticle by nanosuspension method to improve the drug targeting efficiency and also to prolong the duration of action.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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