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# DESIGN, SYNTHESIS, AND CHARACTERIZATION OF SALMETEROL-LOADED POLYMERIC NANOPARTICLES

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**Abstract:**

*Nanoparticles are formulated to target the drug to the specific organ site and to control the rate of delivery of drug. By encapsulating a drug into nanostructures, the being of the drug in the systemic circulation can be prolonged and thus improve perforation into the target tissue and decrease the toxicity. The main aim of this study is to achieve prolonged release of Salmeterol such that the dosing frequency of the drug can be reduced, by which we may decrease the side effects and improve patient compliance. By formulating Salmeterol as nanoparticles, we can directly deliver the drug to the asthma. Investigation of the preparation, characterization, and in-vitro delivery of the nanoparticles was carried out. The different formulations of with different concentrations of drug-polymer and surfactant were examined and finalized. which can accomplish belongings in drug encapsulation and drug delivery kinetics of the nanoparticles.*

**Keywords:** *Salmeterol, polymer, solvent evaporation method, in vitro drug release studies, Zero order kinetics.*

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## INTRODUCTION:

past few decades, there has been a considerable research interest in the area of drug delivery using particulate delivery systems as carriers for small and large molecules [1]. Particulate systems like nanoparticles have been used as a physical approach to alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules [2]. Nanonization technologies have gained special importance due to a steadily increasing number of development compounds showing poor aqueous solubility. [3] Many drug delivery companies and academic research groups have contributed to the currently existing large variety of different technologies to produce drug nanoparticles. [4] These particles consist of pure active pharmaceutical ingredient (API) and are often stabilized with surfactants and/or polymeric stabilizers adsorbed onto their surface. Nanotechnology is the science of the small; the very small. It is the use and manipulation of matter at a tiny scale. [5] At this size, atoms and molecules work differently and provide a variety of surprising and interesting uses. Nanotechnology and Nanoscience studies have emerged rapidly during the past years in a broad range of product domains.[6] It provides opportunities for the development of materials, including those for medical applications, where conventional techniques may reach their limits. Nanoparticles can be classified into different types according to the size, morphology, physical and chemical properties. Some of them are carbon-based nanoparticles, ceramic nanoparticles, metal nanoparticles, semiconductor nanoparticles, polymeric nanoparticles, and lipid-based nanoparticles. The main aim of this study is to achieve prolonged release of Salmeterol such that the dosing frequency of the drug can be reduced, by which we may decrease the side effects and improve patient compliance. By formulating Salmeterol as nanoparticles, we can directly deliver the drug to the asthma

## MATERIALS:

Salmeterol was collected as a gift sample from Hetero Laboratories, Hyderabad. Synthetic polymers, super disintegrants, and other excipients were purchased from AR chemicals.

## METHODOLOGY:

**Formulation development**

**Table-1: Formulation table**

| Ingredients | Formulations | | | |
|---|---|---|---|---|
| | F1 | F2 | F3 | F4 |
| Salmeterol(mg) | 20 | 20 | 20 | 20 |
| Tragacanth (mg) | 50 | 100 | - | - |
| Sodium alginate(mg) | - | - | 50 | 100 |
| Methanol (ml) | 8 | 8 | 8 | 8 |
| Polyvinyl Alcohol(ml) | 10 | 10 | 10 | 10 |
| Water | q.s | q.s | q.s | q.s |

**Method of preparation of Salmeterol loaded nanoparticles:**

Nanoparticles formulations were prepared by solvent evaporation method. The various different amount of polymers was dissolved in solvent mixture of methanol (2 ml) and dichloromethane (8 ml) very slowly on a magnetic stirrer and Salmeterol (5mg) was added to it and the contents were allowed to stand at room temperature for 30 to 45 minutes with occasional vortexing to allow complete solubilisation of drug and polymer. This solution was poured into 5 ml of each different concentration aqueous polyvinyl alcohol solution. The resulting solution was homogenized by using high pressure homogenizer for 3 minutes to form o/w emulsion. This emulsion was immediately added drop wise to 125 ml of aqueous PVA solution. The contents were stirred for 6 hours at room temperature with a magnetic stirrer to evaporate organic volatile solvent, allowing the formation of a turbid nanoparticulate suspension. The suspension was filtered through membrane filter. The filtrate was centrifuged (1000 rpm for 10 minutes) and supernatant

was collected. Further the ultracentrifugation (3200 rpm for 1 hour) was carried for supernatants. Following ultracentrifugation, the pellet was washed and collected two times with deionized water to remove adsorbed drug and was suspended in deionized water to prevent clumping on storage [[7,8].

**FT-IR study [9]**
Compatibility studies of salmeterol and the disintegrants were carried out by using Fourier Transform Infrared Spectroscopy (FTIR). Fourier transform infrared spectra of the samples were obtained in the range of 4000 to 450 cm-1 using a FTIR by the KBr disc method.

**Evaluation of Salmeterol loaded nanoparticles [10,11,12,13]:**
**Particle size:**
All the prepared batches of nanoparticles were viewed under microscope to study their size. Size of liposomal vesicles from each batch was measured at different location on slide by taking a small drop of nanoparticle dispersion on it and average size of nanoparticles were determined.

**SEM analysis**
The morphology of NPs was studied by a scanning electron microscope. For this purpose, the sample was lyophilized and placed on aluminium stubs, and the surface was coated with a layer of gold particles using a sputter coater. The shape of the NPs was determined by scanning electron microscopy (SEM) (XL30, Philips, the Netherlands) at 15 kV and 750 mA.

**Drug encapsulation efficiency:**
Lyophilized nanoparticles 50mg were dissolved in 100ml of phosphate buffer and the drug amount was determined by UV analysis. The encapsulation efficiency was determined as the mass ratio of entrapped Salmeterol in nanoparticles to the theoretical amount of the drug used in the preparation. The entrapment of the Salmeterol nanoparticles was expressed as loading capacity.

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Amount entrapped}}{\text{Total drug.}} \times 100$$

loaded

**In-vitro drug release studies:**
The release studies were carried out using by Franz diffusion cell. It containing 10 ml Phosphate buffer. Phosphate buffer pH 7.4 (100 ml) was placed in a 10 ml beaker. The beaker was assembled on a magnetic stirrer, and the medium was equilibrated at 37±5$^0$C. Dialysis membrane was taken, and one end of the membrane was sealed. After separation of non entrapped Salmeterol dispersion was filled in the dialysis membrane, and other end was closed. The dialysis membrane containing the sample was suspended in the medium. 1ml of aliquots were withdrawn at specific intervals, filtered after withdrawal, and the apparatus was immediately replenished with the same quantity of fresh buffer medium.
The percentage of drug release was determined using the following formula.

$$\text{Perentage drug release} = \frac{Da}{Dt} \times 100$$

Where, Dt = Total amount of the drug in the patch
Da = The amount of drug released

**Stability studies:**
Selected Formulation was subjected to stability studies as per ICH guidelines.
Following conditions were used for Stability Testing.
1. 25$^0$C/60% RH analyzed every month for period of three months.
2. 30$^0$C/75% RH analyzed every month for period of three months.
3. 40$^0$C/75% RH analyzed every month for period of three months.

## RESULTS AND DISCUSSION:

**Drug - excipient compatibility studies (FT-IR):**
The compatibility between the drug and the selected lipid and other excipients was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-lipid mixture, which confirmed the absence of any chemical interaction between the drug, lipid and other chemicals.

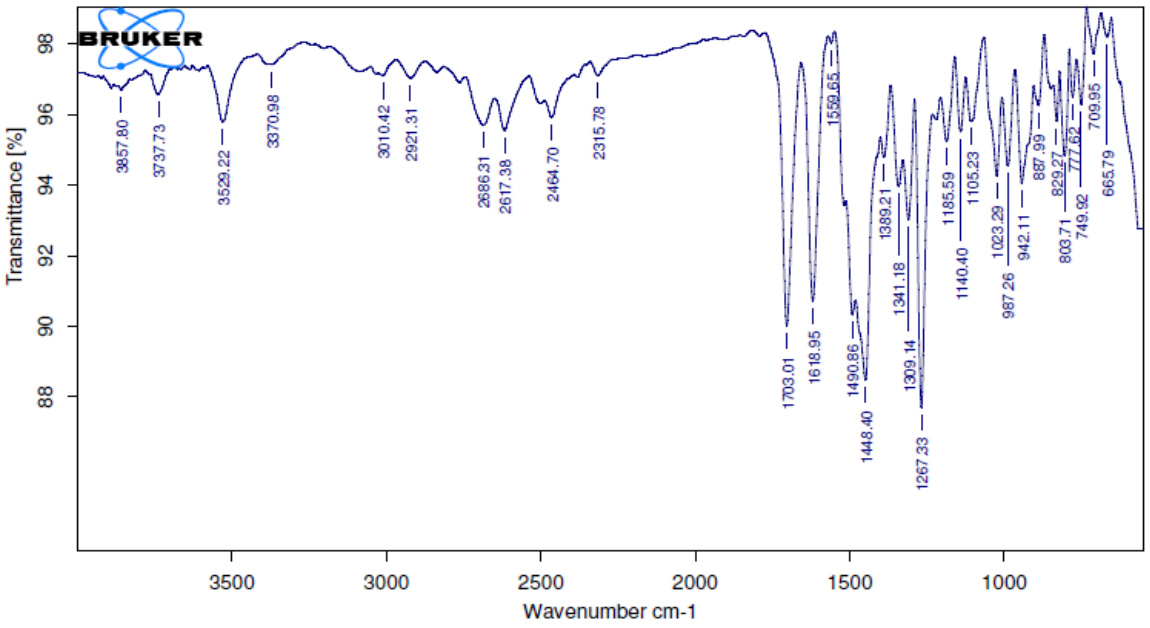


**Fig-:1 FT-IR Sample for Salmeterol**

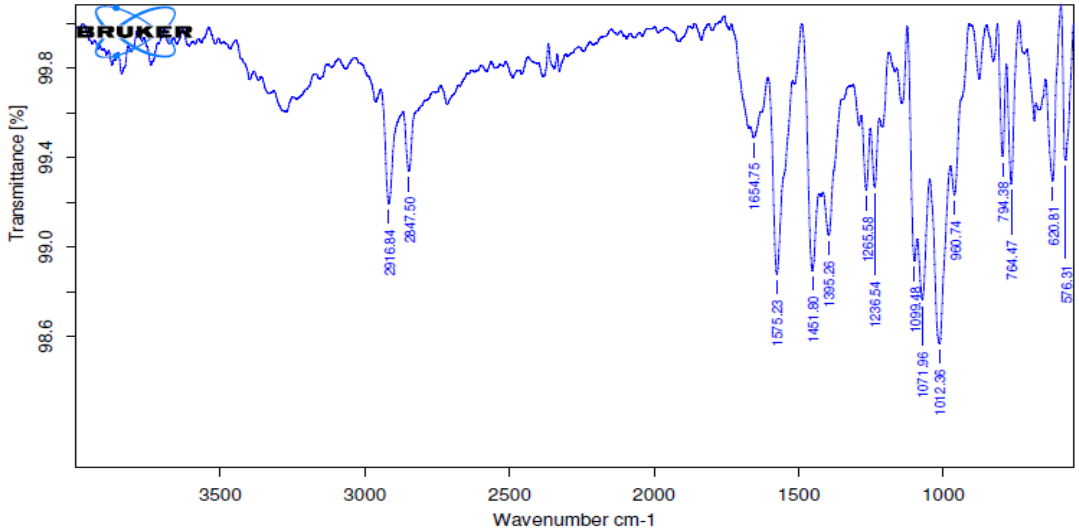


**Fig-:2 FT-IR Sample for Optimized Formulation**

## EVALUATION PARAMETERS:

The nanoparticles prepared were evaluated as per the following parameters-

- Entrapment efficiency
- Particle size and SEM analysis
- In vitro release study
- Drug release kinetics
- Stability studies

**Table: 2 Evaluation Studies of Prepared Nanoparticles: Entrapment Efficiency, Particle size**

| Batch No | Particle size (nm) | Entrapment Efficiency (%) |
|---|---|---|
| F1 | 185.4 | 45.6 |
| F2 | 153.5 | 76.2 |
| F3 | 175.9 | 65.6 |
| F4 | 191.1 | 73.1 |

**Surface morphology:**

Scanning electron microscopy (SEM) SEM revealed that the Salmeterol nanoparticles

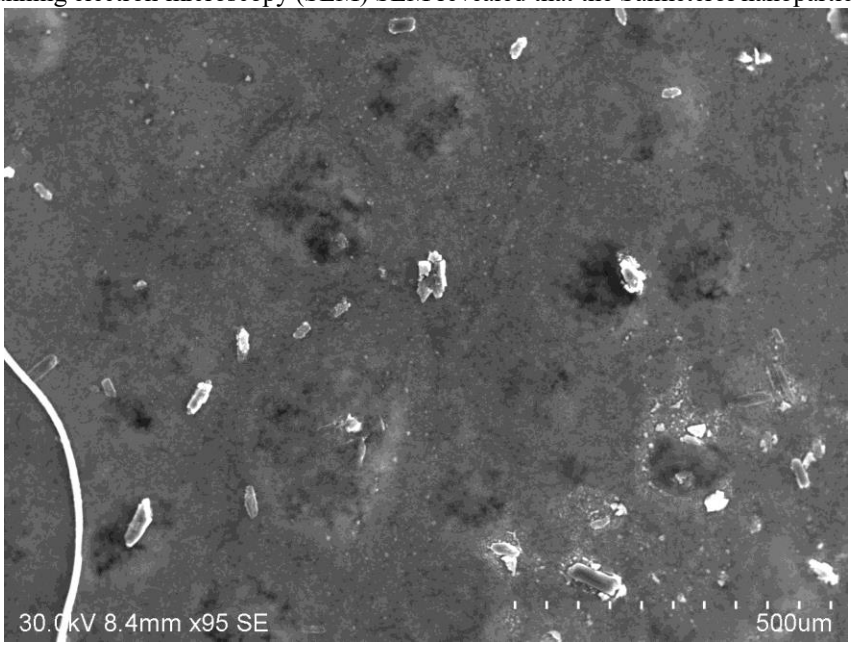


**Fig-:3 SEM analysis of Optimized Nanoparticles**

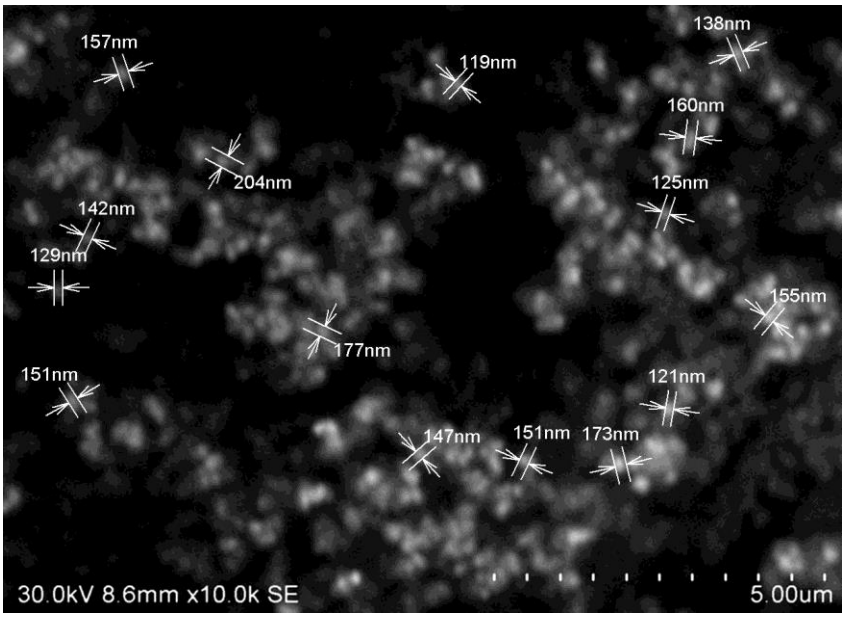


**Fig-:4SEM analysis of Optimized Nanoparticles**

**Drug release studies:**

**Table-:3 Drug release study profiles for all formulations**

| Time (hrs) | F1 | F2 | F3 | F4 |
|---|---|---|---|---|
| **0** | 0 | 0 | 0 | 0 |
| **1** | 33.62 | 32.10 | 31.50 | 32.10 |
| **2** | 40.19 | 39.50 | 40.19 | 39.50 |
| **3** | 49.28 | 52.69 | 47.30 | 52.69 |
| **4** | 62.62 | 61.19 | 61.50 | 61.19 |
| **5** | 70.74 | 71.40 | 69.50 | 71.40 |
| **6** | 78.56 | 82.91 | 75.47 | 82.91 |
| **7** | 92.68 | 92.9 | 89.71 | 92.9 |
| **8** | 93.82 | 98.65 | 92.06 | 95.62 |

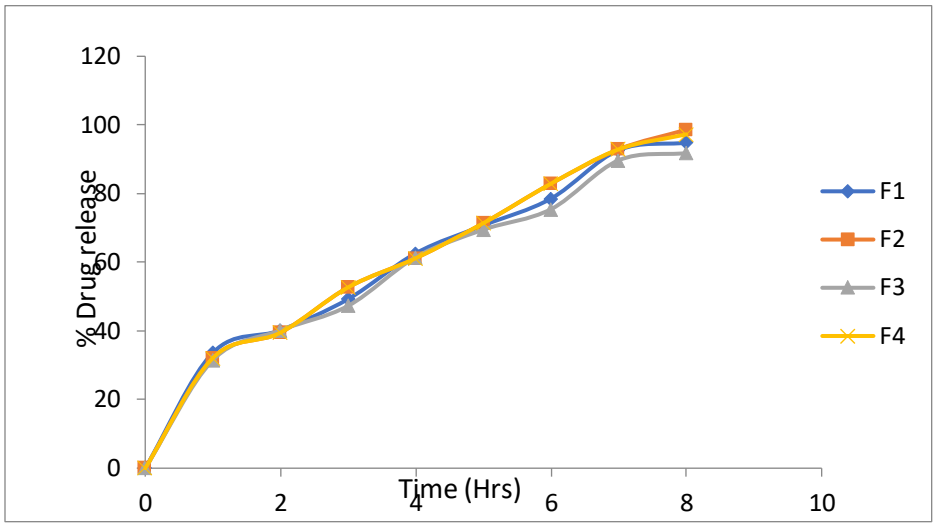


**Fig-:5 In vitro drug release studies for all formulations**

The in vitro diffusion studies were performed in pH 7.4 buffer using Dialysis membrane for 8 hours. Initially the release of drug from all the batches was found to be about 25-35% in 8 hours. This was due to the release of adsorbed drug from the surface of Nanoparticles. Later on a constant and slow drug release was observed for 8hrs. F2 formulation which had drug polymer tragacanth was decided to be the optimized formulation.

**Stability studies:**

There was no significant change in physical and chemical properties of the tablets of formulation F-4 after 3 months. Parameters quantified at various time intervals were shown;

**Table- : 4 Results of stability studies of optimized formulation F-2**

| Formulation Code | Parameters | Initial | 1st Month | 2nd Month | 3rd Month | Limits as per Specifications |
|---|---|---|---|---|---|---|
| **F-2** | **25$^0$C/60%RH % Release** | **98.65** | **96.87** | **96.87** | **96.87** | **Not less than 85 %** |
| **F-2** | **30$^0$C/75% RH % Release** | **98.65** | **96.67** | **96.39** | **96.29** | **Not less than 85 %** |
| **F-2** | **40$^0$C/75% RH % Release** | **98.65** | **96.44** | **96.39** | **96.19** | **Not less than 85 %** |

## CONCLUSION:

The present research proposed a novel formulation Salmeterol Nanoparticles for controlled release. Investigation of the preparation, characterization and in-vitro release of the Nanoparticles was carried out. The different formulations of with various ratios of drug-polymer and surfactant were evaluated and optimised. In this research, in vitro drug release as high as 98.62 has been achieved. The method used for the formulation of Salmeterol containing Tragacanth and sodium alginate nanoparticles was solvent evaporation method followed by sonication to reduce the particle size.

Nanoparticles formulations showed good results in terms of the assayed drug content and encapsulation efficiency. This indicates that the method used for the formulation produced good yield and it was suitable and reproducible in nature. Formulation (F-2)showed the highest encapsulation efficiency. Permeation studies with dialysis membrane were carried out as per the method reported. The formulations showed good drug release from the polymer, the *in vitro* drug release profiles of all the formulations are with in limits.

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