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A Review on Formulation and Evaluation of Dry Powder Inhalation

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ABSTRACT: DPI is the device that delivers the medication to the lungs in the form of a dry powder. People who have chronic obstructive pulmonary disease (COPD) or other lung conditions often take their medications using such devices.DPI are popular for pulmonary drug delivery.[1]Various techniques have been employed to produce inhalable drug particles and improve the delivery efficiency of DPI formulations. Physical stability of these DPI formulations is critical to ensure the delivery of a reproducible dose to the airways over the shelf life.[2]Present research is aimed to develop and characterize a sustained release dry powder inhalable formulation of salbutamol sulphate. The Salbutamol sulphate Microparticles were prepared by solvent evaporation method using biodegradable polymer poly(D,L- Lactic-co-glycolic acid) to produce Salbutamol sulphate microparticles mixed with carrier respirable grade lactose for oral inhalation of dry powder. The drug content were estimated to produce 1 mg sustained release Salbutamol sulphateper. Total four formulations K1, K2, K3, K4 were prepared with 1:1,1:2,1:3,1:4 ratio of salbutamol sulphate: poly(D,L- Lactic-co-glycolic acid) The developed formulation were studied for physicochemical properties. The prepared formulations effectively releases drug for 12 h in diffusion bag studies. Based on dissolution performance the 1:1 ratio of salbutamol sulphate: poly (D,L – Lactic-co-glycolic acid) produces invitro release 92.57% at 12 hour and having particle size of microparticles 5.02 ± 0.6 and the pulmonary deposition of dry powder 34.5±3.21(respiratory fraction in percentage).[3]

KEYWORDS: Salbutamol,sustained release,dry powder inhaler, Microparticles

I. INTRODUCTION

What is dry powder inhaler? Some medications can be taken in the form of a dry powder, using a dry powder , which is a handheld device. A DPI delivers medication to the lungs as you inhale through it. It doesn't contain propellants or other ingredients it just contain Your medication.DPI is the device through which a dry powder formulation of an active drug is delivered for local systemic effect via the pulmonary route. DPI doesn't push the medication into your lungs you have to breath in strong and steady to get the medicine.

Early dry powder inhalers were designed for low drug doses in asthma and COPD therapy. Nearly all concepts contained carrier based formulations and lacked efficient dispersion principles. Therefore, particle engineering and powder processing are increasing applied to achieve acceptable lung deposition with this poorly designed inhalers.[4]

1.Dry powder for Inhalers: Dry powder inhaler have been available commercially since approximately 1970, although the earliest prototypes were described several decades earlier DPIs contain a powder formulation, which most frequently consists of an ordered mixture of microionized drug (<5 micron in diameter) and larger carrier lactose particles that are required to improve powder flow properties. The patients inhalation through the device is used to disperse the powder and to ensure that some of the dose is carried into the lungs. An alternative type of formulation used in some DPIs consists either of microionized drug particles alone loosely aggregated into small sphericals or of cospheronized drug and lactose.

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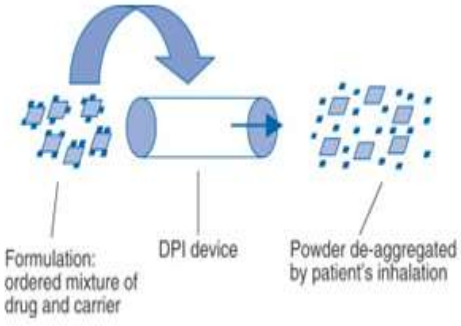

Figure 1.1 Principle of operation of a dry powder inhaler (DPIs)

The formulation most frequently consists of an ordered mixture of microionized drug and carrier lactose, which is de-aggregated by the patient's inhalation through the device.[5]

DPIs are basically of three types:

1) Unit- dose devices:

In which an individual dose in an gelatin capsule or blister is loaded by the patient immediately before use.[5]Early devices were all unit- dose systems and were dependent on loading and triggering procedures.[6]DPIs were single dose units containing microionized drug blended with lactose carrier particles in a single gelatin capsules to be inserted in to the device by the patient immediately before inhalation use.Rotahaler ,spinhaler,cyclohaler/aerolyser were well known single dose powder inhaler. In rotahaler device capsule inserted and broken into two halves by twisting the mouthpiece. The powder falls intothe body of the Inhaler and patient Inhale through the mouthpiece to scatter the powder and deliver small quantity of the microionized drug particles into the lungs. The powder properties played active role in this inhalable powder formulation for the deposition to the deep lung depends based on particle size, shape, morphology and density. The biocompatible excipients selection was considered as must to produce a desired dissolution and the improved deposition of desirable particles in to the mini airways of the lungs.[3]

2) Multiple unit- dose devices:

Which contain a series of blisters or capsule;[5]employs individual doses that are contained within blisters (four or eight blisters are standard) on a disc(Islam and Gladki,2008;. Noakes,2002). Once the device is actuated, a needle pierces the upper and lower surfaces of a blister, and on inhalation by the patient, the blister is dispersed into the airstream (canada, 2010). The drug effectively dissociates from the carrier with a fraction of the dose being delivered to the lung; then the disc re- primes by rotating to expose the next blister.[6]

3) Reservoir devices :

In which powder is metered from a storage unit by the patient before inhalation. DPIs contained all the doses in a bulk reservoir, with the dose dispensed through manipulation of the device before inhalation (Smith and Parry- Billings 2003). Rotating the conical cavity release the drug into the airstream and disperse it into the inhalation channels , which are helical in shape to induse turbulent airflow.[6]

Figure1.2 : Types of Inhaler Devices

II. MATERIALS AND EQUIPMENTS

Sr.no.	Materials	Source
1	Salbutamol sulphate	Fourrts India laboratories Pvt Ltd Chennai
2	Poly (lactic co glycolic) acid	Brimingham polymer INC USA
3	Polyvinyl alcohol	Orchid pharmaceutical Chennai
4	Methanol	Qualigens Mumbai
5	Dichloromethane	Qualigens, Mumbai
6	Acetonitrile	Qualigens Mumbai
7	Potassium dihydrogen orthophosphate	SD fine chem Ltd Mumbai

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8	Sodium chloride	SD fine chem Ltd Mumbai
9	Sodium hydroxide	SD fine chem Ltd Mumbai

Table 2.1 Material and source

Sr.No	Equipments
1.	Probe sonicator
2.	Homogenizer
3.	Centrifuge
4.	Spectrometer
5.	Scanning electron microscopy
6.	Particle size analyser

Table 2.2 Equipments

III. METHODOLOGY AND EXPERIMENTAL WORK

a) Preparation of Microparticles:

Solvent Evaporation Method:

The solvent evaporation method involves preparation of o/w emulsion between organic phase consisting of PLGA (50:50 ; 45KD) in Dichloromethane DCM to this mixture Salbutamol sulphate Solution was added and mixed by sonication using probe sonicator and injected this mixture dropwise into the aqueous phase containing 2% w/v PVA. The organic phase was emulsified in aqueous phase by homogination at 10 000 rpm For 10 min using a homiginzer (viritis cyclone IQ, USA). The emulsion was stirred for 12 h at 25±2° using magnetic stirrer to ensure complete evaporation of dichloromethane. The microparticles thus prepared were recovered by centrifugation (15000 rpm, 20 min 4°). The precipitate was washed completely removed polyvinyl alcohol. The product dispersed in cold water and recovered by lyophilisation. The 4 different batches of microparticles were prepared by keeping organic phase to aqueous phase ratio as (OP:AP::1:5) and varying drug: polymer ratios of table 1.

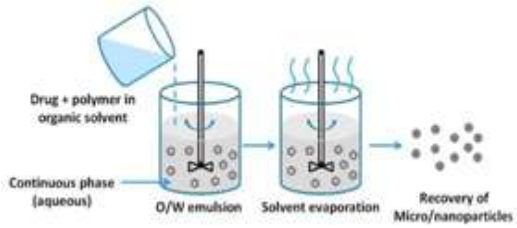

Figure 3.1 : Preparation of Microparticles

Formulation code (mg)	SS: PLGA	Weight of salbutamol sulphate (mg)	Weight of PLGA (mg)
K1	1:1	50	50
K2	1:2	50	100
K3	1:3	50	150
K4	1:4	50	200

Table.3.1 : formulation of salbutamol poly (lactic co glycolic) acid microparticles

Volume ratio of OP : AP = 5 ml (1.5), DCM: Dichloromethane, PLGA:poly(Lactic-co-glycolic), SS: Salbutamol sulphate,PVA : Polyvinyl alcohol, OP: organic phase,AP: aqueous phase.

b) Dry powder inhaler preparation:

The physical mixture of microparticles with coarse carrier lactose inhalable grade lactohale to enhance aerosol properties for the production of respirable salbutamol sustained release powder for Inhalation.[3]

EvaluationTest:

1)Fourrts transform infrared spectroscopy:

Infrared spectroscopy was used to determine various functional groups of the drug molecule. In general the functional groups can exhibit changes as a result of processing drug formulations.The resulting FTIR spectra graphs of salbutamol sulphate, and Trials K1, K2, K3 and K4.

2) Scanning electron microscopy:

The surface morphology and shape of the prepared microparticles were investigated with scanning electron microscopy (VEGA3 LMU, TESCAN) with a maximum magnification of 10 00 000*X and resolution 3 nm at maximum applied voltage of 30 kV. The electronic images were recorded digitally at heigher magnification. Scanning electron microscopy was used to

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visualize the particle diameter structural and surface morphology of the DPI microparticles. The powder were kept on adhesive coated, 6.25 mm radius aluminium stubs.

The remaining powder was removed by tapping the stub and blowing a jet of particle free compressed gas. Then the specimen were examined in the scanning electron microscopy which will operated with maximum vaccum and with accelerating voltage of 5- 15 KV with a specimen working distance of 12 min.

3) Entrapment efficacy :

The drug content were determined from the microparticles. The SS was extracted from microparticles with sodium hydroxide (0.1 M) after dissolving the microparticles in acetonitrile. After suitable dilutions, the SS content was measured in a UV/V is spectrophotometer (jasco) at 278 nm. Entrapment efficacy was calculated using the following formula :

Entrapment efficacy= (estimated% drug content)/(% drug contenttheoretical)× 100

4) Percent yield :

The percentageyield was calculated using the following formula. Percentage yield= (Actual wt. Of microsphere)/ (wt. Of starting material) × 100

5) Particle size determination :

The laser diffraction method was used to estimate the particle size of microparticles. The helos particle size analyser vibro/ Rodos drug dispersion system:

Sympatec Gmbh system were used to measured particle size. Roughly 100 mg of the powder was used to achieve the required obscuration of 5 %. The particle size data obtained were represented as D0.5

6)In vitro drug release study:

The in vitro dissolution of salbutamol sulphate from the microparticles wereanalysed by a dialysis bag diffusion method. The invitro release was carried out with phosphate buffer saline(PBS) pH 7.4 as the diffusion medium and a dialysis membrane of 14 kDa molecular weight was used. An aqueous dispersion equivalent to 10 mg of salbutamol sulphate microsphere was kept in a dialysis bag and sealed at both ends. The dialysis bag was immersed in 250 ml of diffusion medium and stirred at 100 rpm. Sample were withdrawn at predetermined time interval, and the receptor phase was replenished with an equal volume of blank after each sample was withdrawn. Samples were filtered through 0.46micron filter and approximately diluted with pH 7.4 PBS . Absorbance of the samples at 278 nm was determined by UV/V is spectrophotometer with pH 7.4PBS as blank. The cumulative percent drug at various time interval was calculated and plotted against time. All experiments were done in triplicate.[3]

IV. RESULT

Evaluation Test:

1)FTIR Spectroscopy

Fourier transform infrared spectroscopy was performed on pure drug and formulation K1,K2, K3 AND K4. No difference in the position of absorbance bands was observed in the spectra of salbutamol sulphate and formulation, indicating no chemical interaction between the drug and polymerin solid state. Spectra of salbutamol sulphate showed sharp band at wavelength of about 1000cm-1, while spectra of formulation also show bands at same wavelength, but somewhat less intense due to drug polymer complex. This indicated less probability of chemical interaction of drug with other excipients. All the microspheres were smooth almost spherical in shape and non porous.

2)Characteristics of microparticles

Formulation code	Drug polymera	Mean±SD	
		Particle size	Entrapment efficacy
K1	1:1	5.02±0.6	78.70±0.06
K2	1:2	4.69±0.7	76.50±0.04
K3	1:3	4.86±0.4	77.30±1.20
K4	1:4	4.79±0.3	77.60±1.84

Table 4.1 : physical characteristics of microparticles

The particle size, and entrapment efficacy were evaluated for microparticles as given in Table 3. The mean particle size of microparticles ranged from 4.79 to 5 µm of all four trials. Entrapment efficacy found to be 77-78% for all four trails varied slightly with the various proportion of polymer. The dissolution was carried out in PBS at pH 7.4 at 37° ± 0.5°. The drug released at 12 h of formulation trails were as follows: K1,92.57%, K2,81.92% ; K3,78.42%; ANS K4, 77.71%. The

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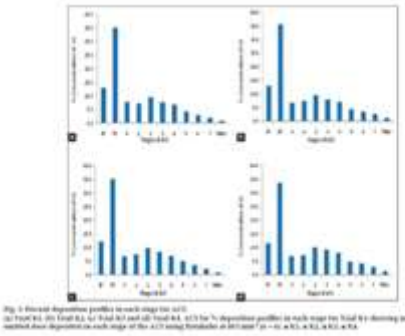
drug release were found to be not less than 77% at 12h in all trails. The fig. 4 represent, cumulative percent drug release versus time in hour for trails K1- K4. It was understood that the drug release versus time was the linear curve and shows sustained release of SS in all formulations trials of K1 to K4. Among the four trials, formulation of K1 exhibit Better drug release over other trials K2-K4. Thereby 1:1 ratio of drug : polymer exhibited as best dissolution result.[3]



V. SUMMARY AND CONCLUSION

DPI can be considered as an attractive drug delivery system, both for drug that are to be administered for local therapy in the lungs, as well as for drugs that are to be administered for local therapy in the lungs, as well as for drugs that act systemically and for which the lungs is only port of entry to the body. Currently, the inhalation performance of DPI is being improved by changing formulation strategy, drug an carrier particle engineering.

The future research in the DPIs will thus aim to assimilate drug in a matrix particles to achieve specific pulmonary drug deposition and probably to achieve intracellular drug delivery especially, protein, peptide, plasmids, DNA etc. A better understanding of the influencing properties of powder on the performance of DPI will help to adress the challenges in the development of DPI formulation and Inhaler devices for optimum therapeutic benifits.

A range of DPI s is already marketed, and many others are in development. Not all new DPI devices and formulations will reach the market, but many of those that do are likely to have successfully adressed perceived limitations in earlier systems. As we go forward into the 21st century, DPI delivery system are likely to contribute significantly to successful drug delivery by the inhaled route, not only to treat asthma, but also to deliver a wide range of drugs intended both for local and systemic applications.

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