

Journal of Pharmaceutical Advanced Research**(An International Multidisciplinary Peer Review Open Access monthly Journal)**Available online at: www.jparronline.com**Formulation, Optimization, and Characterization of Spray-Dried Triamcinolone Acetonide Loaded Dry Powder Inhaler for Pulmonary Delivery****Km Nandani Jayaswal, Dilpreet Singh^{*}, Ghanshyam Das Gupta**

Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India.

Received: 08.07.2020

Revised: 15.07.2021

Accepted: 20.07.2021

Published: 31.07.2021

ABSTRACT: Background: In dry powder inhalers (DPIs), a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. Successful delivery of drugs depends on the integration between powder formulations and the device performance. **Aim:** The aim of the present work is to develop and characterize spray-dried formulation of Triamcinolone Acetonide (TMA) loaded dry powder inhaler for pulmonary delivery. **Method:** The microparticles were prepared and optimized by the solvent evaporation method using poloxamer-188, β -cyclodextrins and polyvinyl alcohol. The final formulation was loaded with the TMA drug and 1, 2-Dipalmitoyl-sn-Glycero-3-Phosphocholine (DPPC). The dry powder inhaler was prepared by the spray-dried techniques and the formulations were characterized for Particle size, surface area measurement, and Scanning electron microscopy (SEM). The *in-vitro* studies were performed and drug release data were compared with pure drug (TMA) and final formulation of dry powder inhaler. **Result:** The particle size was micron size and SEM study revealed that the particle morphology was spherical shape and free flowing. The drug content was found to be good (98 %). The drug was released in a controlled manner with zero order kinetics. The FTIR study revealed that there was no drug excipient interaction. The X-RD study concluded that no crystallinity of drug was formed in due course of preparation of PDI. **Conclusion:** The optimized TMA-loaded DPI could be successfully therapeutically used for asthma and delivery through pulmonary delivery. The TMA was a corticosteroid drug used as an anti-inflammatory for pathological conditions like asthma.

Corresponding author*

Dr. Dilpreet Singh
Associate Professor
Department of Pharmaceutics,
ISF College of Pharmacy,
Moga, Punjab-142001, India
Tel: +91-8054412803
E. mail ID: dilpreet.daman@gmail.com

Keywords: Dry powder inhaler, Triamcinolone Acetonide, spray dried, DPPC, Poloxamer-188, Beta-Cyclodextrin, *in-vitro*.

INTRODUCTION:

Asthma is a chronic inflammatory syndrome of the airways that is generally characterized by airway hyper-responsiveness and changeable airflow obstruction. It can be naturally cured or reversed^[1]. Allergen sensitization is a substantial asthma risk factor, and asthma incidence has grown in lockstep with allergy prevalence in all nations over the last 40 years^[2]. Anti-asthmatic medications can be provided in a variety of ways, although there are other options, such as

parenteral or oral (prednisone), the pulmonary route is frequently used since it allows the medicine to be administered directly to the site of action where it's required. Antiasthmatic therapies differ depending on the severity of the condition, but most consist of a combination of β -2 adrenergic agonists and corticosteroids for immediate relief. Levalbuterol, metaproterenol, terbutaline and albuterol are β -2 adrenergic agonists for Bronchodilators that help to relax airway muscles within 5 min. They cause an increase in airflow, making it easier for the patient to breathe. For 3 to 6 h, β -2 adrenergic agonist help relieve asthma symptoms. Anti-inflammatory corticosteroids like flunisolide, fluticasone furoate, beclomethasone are utilized and require multiple injections per day. Inhaled corticosteroids are effective in the treatment of asthma because they can interfere with several inflammatory processes involved in asthmatic pathophysiology [2-4]. When opposed to the systemic approach, Inhalation therapy has benefits in the treatment of asthma caused by corticosteroids. It assists in the efficient and optimum treatment of a condition that needs the administration of large doses of active ingredients via the systematic approach [5,6]. However, due to respiratory maintenance systems, these advantages are frequently accompanied by narrow deposition in the lungs and a brief duration of effect [7]. As a result, the ideal inhaled corticosteroid should have a long residence time in the lungs, intrinsic action, poor oral bioavailability and high systemic clearance, with minimal systemic adverse effects. Most commercially marketed inhaled corticosteroids, on the other hand, still required many daily dosages [8-10]. To modify the duration of corticosteroid residency in the lungs, an effective formulation for delivering corticoids to the lungs can be developed. Nebulization of medication solutions or nanoparticle suspension can be used to deliver the drug to the lungs, as may metered dose inhalers or dry powders for inhalation [11-14]. Because this corticosteroid is frequently used as a reference to evaluate the efficacy of other compounds, the decision was made to use a Dry powder inhaler to use a Triamcinolone Acetonide.

There is biocompatibility, biodegradability, and an increase in the pulmonary surfactant ability to form porous particles, dipalmitoyl-sn-glycero-3-phosphatidylcholine (DPPC), beta- cyclodextrins, and poloxamer-188 were chosen as excipients and polymer [15-17]. Triamcinolone Acetonide encapsulation into DPPC-beta cyclodextrins and poloxamer-188

microparticles were optimized by spray drying, changing the concentrations of poloxamer-188 and Beta-cyclodextrin relative to the PVA. The dry powder inhaler physicochemical characterization, as well as effectiveness using an SEM, X-RD, and drug release in sink circumstances, will be shown. The aim of this work is therefore to develop and characterize the Triamcinolone Acetonide drug loaded dry powder inhaler for treatment of asthma. The prospect that a corticosteroid will be delivered will allow the substance to reside in the lungs for a longer time [18].

MATERIALS AND METHODS:

Triamcinolone Acetonide was Provide by Sun Pharmaceutical, Tandalija, Vadodara. 1, 2-dipalmitoyl-sn-glycero-3-Phosphatidylcholine (DPPC) was Provide by Avanti Polar Lipids, Inc., India. The β -Cyclodextrin and Poloxamer-188 were purchased from Himedia, India. The Polyvinyl Alcohol (COLD) was procured from CDH Laboratory Reagent. All of the chemicals utilized were of the highest analytical quality. Organic solvents were provided by SDFCL Grade.

Preparation of Microparticle:

Firstly, the prime variables of DPI have been optimized like polymer and stabilizer concentration in the presence of precipitation base (PVA) using the conventional solvent extraction technique. Briefly, Poloxamer-188 was dissolved in water and β -cyclodextrin was solubilized in Dichloromethane. Both phases were mixed in a single beaker under magnetic stirring.

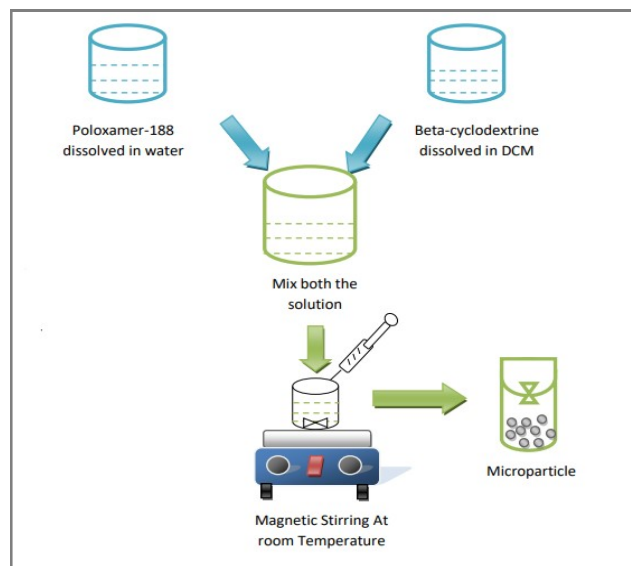


Fig 1. Schematic diagram for the preparation of optimized microparticle by solvent evaporation method.

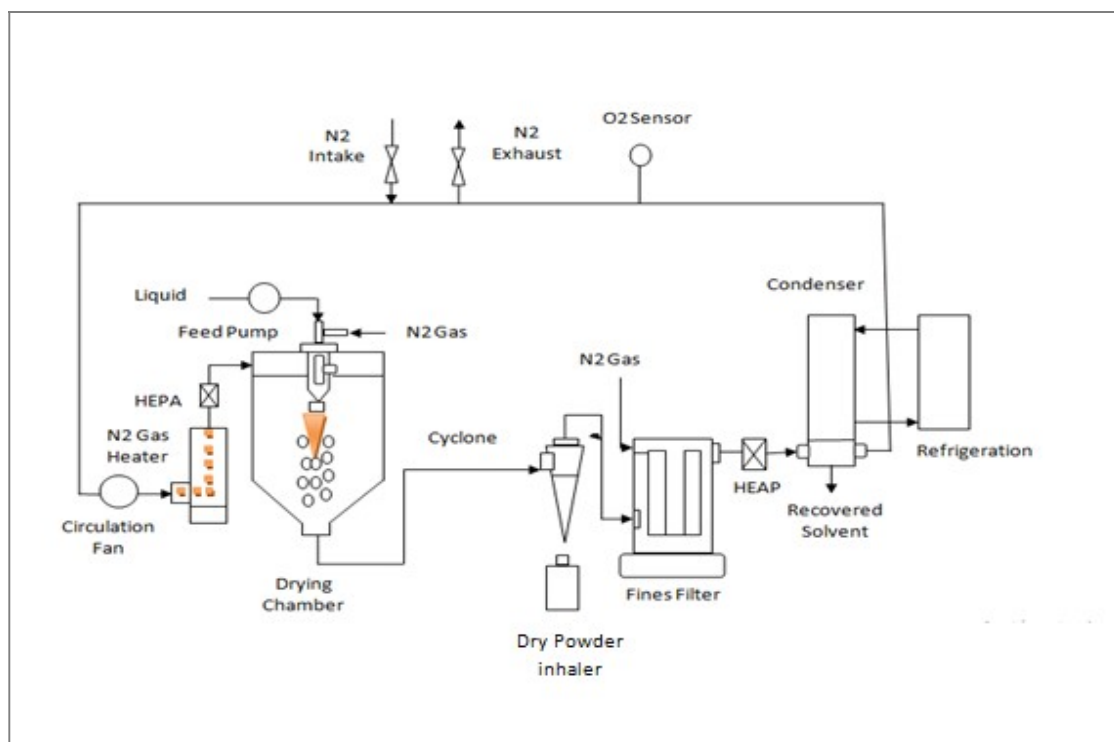


Fig 2. Preparation of Triamcinolone Acetonide loaded DPI through the Spray dried method.

Simultaneously, polyvinyl alcohol (0.5 g) was dissolved in water to prepare a 0.5 % w/v concentration using a magnetic stirrer. After that organic and aqueous phases were then filled in a hypodermic syringe and then injected drop wise in a PVA solution. The solution was kept overnight for complete evaporation of the solvent, afterwards, the resultant microparticle was filtered and dried at a hot air oven (IIC – 101, Sima Labs, New Delhi) at a temperature of 60 °C. The preliminary batches were prepared and then characterized to obtain an optimized batch that was further utilized for spray drying^[19]. The schematic presentation for preparation of microparticles by solvent evaporation method is given in Fig 1.

Preparation of DPI based formulation of TMA:

For spray drying, the quantities of Poloxamer-188 and beta-cyclodextrin were optimized in the previous method. During the experiment, Beta-Cyclodextrin was dissolved in water and Dipalmitoylphosphatidylcholine (DPPC) and the drug were dissolved in ethanol. The mixture of ethanol (70 ml) and aqueous solution (30 ml) was then combined in a 70: 30 % v/v ratio and spray dried (Laboratory Spray Dryer – LSD 48, Jisl, Mumbai) under the following conditions. Temperatures of 130 and 40 °C in the inlet and outlet in that order are ultimate. The solution was passed through a 0.7 mm fluid nozzle

with a feed flow rate and aspirator speed of 1 ml/min and 100 m³/h, respectively. Afterward, the resultant powder was collected and evaluated for *in vitro* characterization studies^[20]. The schematic presentation for preparation of DPI by spray drying method is given in Fig 2.

CHARACTERIZATION:

Particle size distribution:

The particle size of Powder size distributions was investigated with a particle size analyzer DLS 4 C Beckman Coulter. The findings were represented in conditions of particle sizes at 10, 50, and 90 % of the total volume distribution as D10, D50 and D90 respectively. The equation 1 was used to put the volume distribution's range; the breadth of the distribution in respect to the median diameter is a measure of the breadth of the distribution (1). A large span indicates a more varied size distribution. The values shown are the average of at least three different determinations^[21].

$$\text{Span value} = (D10 - D90)/D50 \dots\dots(1)$$

Flow properties of powder:

The DPI formulation has excellent flow properties characteristic of the drug-carrier combination. The Angle of repose, bulk density, Carr's index, and Hausner's ratio was among the flow attributes of powder

tests done on a mixture of microparticles with spray-dried^[21].

Tap density and aerodynamic diameter:

Using a tapping instrument, the powder tap density (ρ) was calculated (Pharma test PT-TD1). Powder samples were exactly weighed and put into a 5 ml graduated cylinder, after the 1000 time taps, the height was measured, allowing the density to plateau^[22]. Due to space between particles, the tap density of monodisperse spheres, assuming effective packing, is roughly a 21 % underestimation of the true particle density. The polydispersity reduces the space between particles; this is likely offset by improper packing^[23].

Surface Area Analysis:

The BET gas adsorption technique was used to evaluate the surface area of optimized microparticle and spray-dried formulation of dry powder inhalers. The powdered samples that had been produced under vacuum for 1 h at 40 °C under BET surface area analyzer (Micromeritics ASAP, UK). The BET multipoint approach was used to calculate the specific surface area^[24].

Drug content of dry powder inhalers:

To determine the TMA content, an accurately weighted 100 mg mixture of Novel formulation DPI was dissolved in a 50 ml phosphate buffer (pH 7.4) solution. The solution was stirred on a magnetic stirrer for 1 h. This solution was then stored for another 24 h. Then the solution was stirred, filtered, diluted and analyzed for drug content at 239 nm using a UV-visible Spectrophotometer-1700 Pharma Spec.^[24]

FTIR (Fourier-Transform Infrared Spectroscopy):

The instrument of Nicolet-380 was used to conduct Fourier-transform infrared spectroscopy (FTIR) study to test TMA and DPI. The particle powder was placed on the diamond ATR crystal, which was then clamped in position and sealed with a glass cover slip. The ATR crystal and IR spectra were obtained between 700 and 4,000 cm^{-1} with an 8 cm^{-1} spectral resolution. Varian Resolutions software was used to compile and interpret the data^[25].

Scanning electron microscopy:

The surface morphology of pure drug TMA and final formulation of DPI were determined by using SEM (SEM-VL10, USA). A filament of current, roughly 0.5 mA and a voltage range of 1 to 3 kV was used for scanning

electron microscopy (SEM). A Cressington sputter-coater 208HR with a rotary planetary-tilt stage and an MTM-20 thickness controller was used to deposit powder samples on carbon conductive double-sided tape and coat them with a palladium-platinum layer of around 4 nm^[26,28].

X-RD analysis:

The identification of crystallite of pure drug TMA and the spray-dried formulation of DPI were determined using XRD studies. A dichromatic XRD (Hitachi-01LV) operating at 40 kV and a current of 30 mA with Cu K radiation within the range was used to produce X-ray diffraction patterns of pure drug and drug-loaded dry powder inhaler formulations^[21].

In-vitro dissolution studies:

In vitro drug release of pure TMA and optimized DPI formulation were carried out using Phosphate buffer saline as standard dissolution media in USP Type II Dissolution Apparatus. TMA (Pure) and optimized spray-dried DPI formulation equivalent to 10 mg TMA were added in the dissolution vessel preloaded with Phosphate buffer saline. The entire experiment was run at a revolution speed of 50 RPM and a temperature of 37 ± 0.5 °C. At predefined time intervals of 0, 0.15, 0.3, 1, 2, 4, 6, 8, 12, 24 and 48 h, an aliquots of 5 ml drug solution were collected in test tubes and filtered through a filter membrane of 0.22 μm . After each sampling, an equal volume of fresh dissolution medium was filled to maintain sink conditions. The filtrate was appropriately diluted with methanol and drug release was quantified spectrophotometrically at 239 nm^[20,27].

RESULTS:

The Laser light diffraction method was used to determine the particle size of DPI formulations. The particle size of the optimized microparticle formulation (F1) was the best particle size that is 0.566 μm and PDI 0.255, as shown in Table 1, and the particle size of spray dried final formulation of DPI was 2.003 μm and PDI 0.772 for targeted of pulmonary delivery. The spray-dried formulation of Dry powder Inhaler determined the % yield of Dry Powder Inhaler, Tapped densities, Carr's

Table 1. Concentration of optimization batch microparticle, Particle size determination and PDI.

Formulation Batch	Poloxamer-188 (mg)	β -CD (mg)	PVA (g)	Avg. Particle size (μ m)	PDI
F1	700	200	0.5	0.566	0.255
F2	600	50	0.5	0.725	0.316
F3	700	50	0.5	2.063	0.798
F4	100	200	0.5	2.995	1.097
F5	100	50	0.5	0.706	0.296
F6	700	200	0.5	1.803	0.799
F7	100	50	0.5	2.412	0.943
F8	100	200	0.5	1.236	0.100
F9	200	50	0.5	0.630	0.225

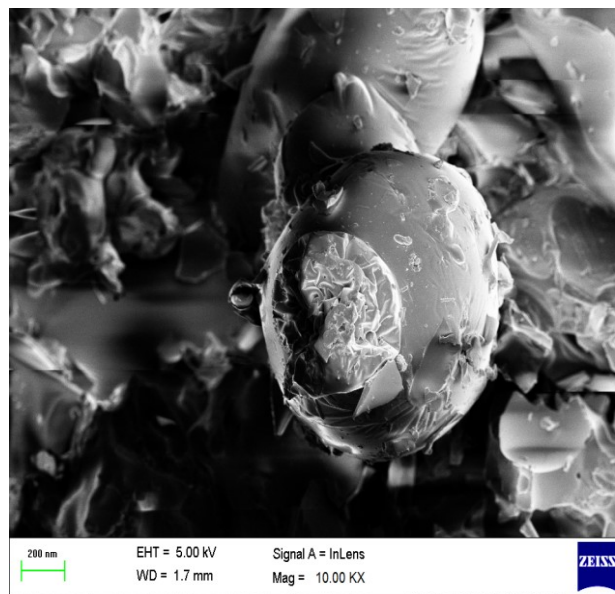
OVA – Polyvinyl alcohol, β -CD – Beta cyclodextrine and PDI - Dry powder inhaler.

index, Hausner's ratio, Angle of repose, surface area and Drug content of dry powder inhaler were evaluated. The result was shown in Table 2.

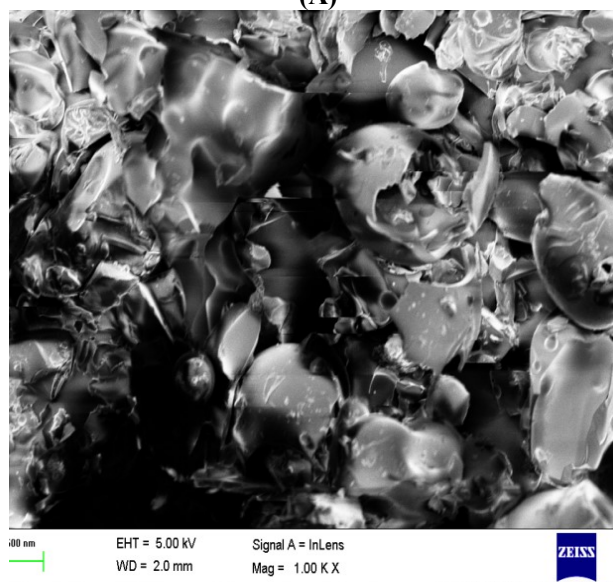
Table 2. Dry powder inhaler flow properties.

Parameter	Results
Yield (%)	295.4 m ² /g
Tapped density	0.91 g/cm ³
Carr's index	13 %
Hausner's ratio	0.14-1.15
Angle of repose	26.3 °
Surface Area	295.4 m ² /g
Drug Content	89.9 %

The pure drug TMA and final formulation IR spectra were shown in Fig 3. The variation of stretching vibration was frequently seen in the Frequency Range 3500 to 1000 cm⁻¹, showing C-H deformation. The surface structure and particle morphology of the Pure drug and Final formulation of DPI shown in Fig 4, SEM images are free-flowing particles and spherical in the shape of the TMA and DPI. The X-ray powder diffraction of the pure drug TMA and final formulation of DPI was determined by the Sharp and intensive peaks shown in Fig 5. The TMA release from 10 % of the DPI microparticle was followed by time in 48 h shown in Fig 6. The burst effect of the concentration of 1 g/ml and the fasten release was observed in 48 h. From the powder, 30 % of the drug was released and from DPI, the drug released was 70 % in 48 h. The Fig 7 was showed the final formulation dry powder inhaler to follow Zero-order kinetics because of a higher R² value i.e. 0.973 when compared with the Higuchi model, Hixson model, Korsmeyer-Peppas model and First-order kinetics.



(A)



(B)

Fig 4. SEM microscopy of A) TMA and B) TMA loaded DPI.

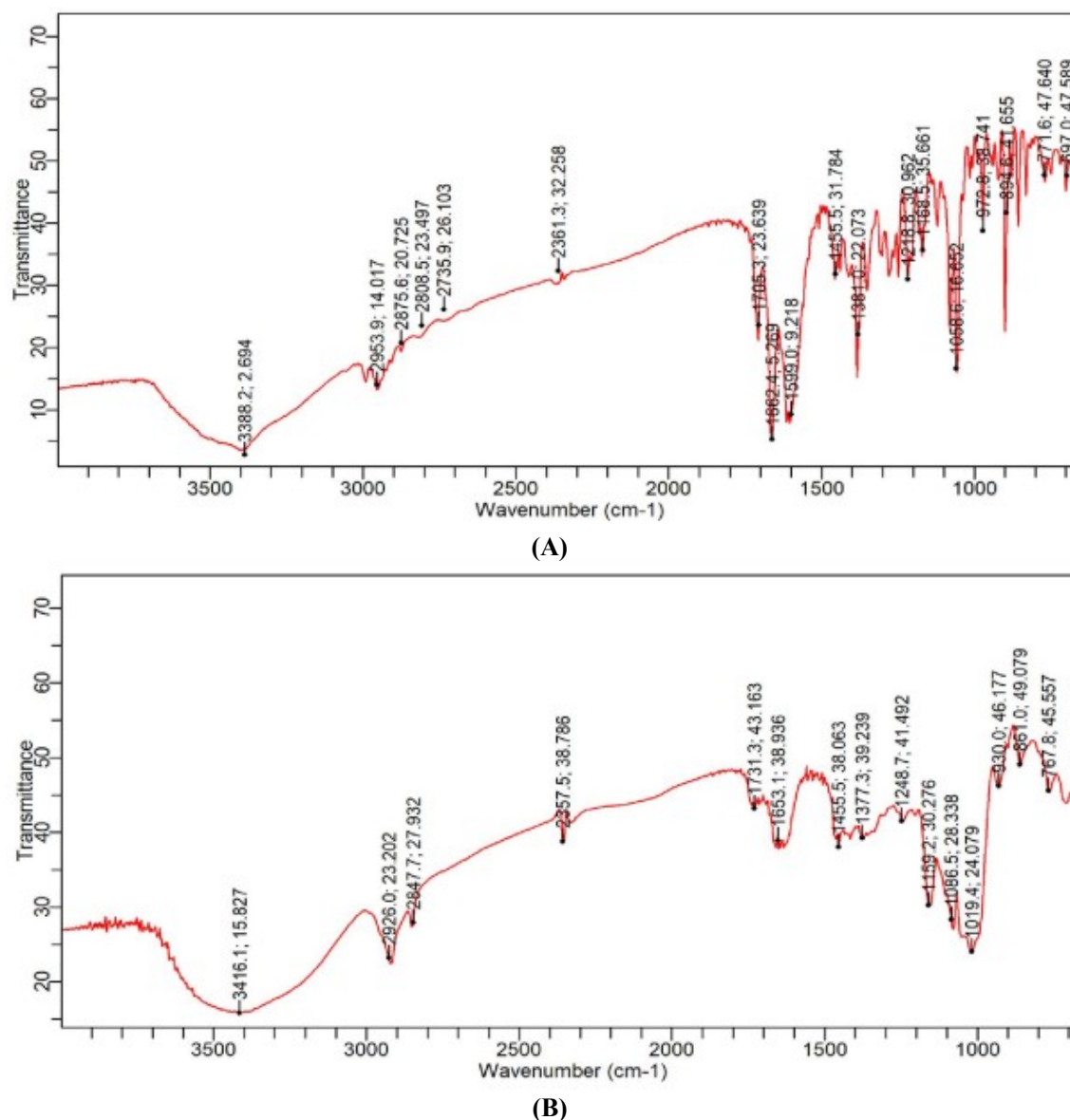


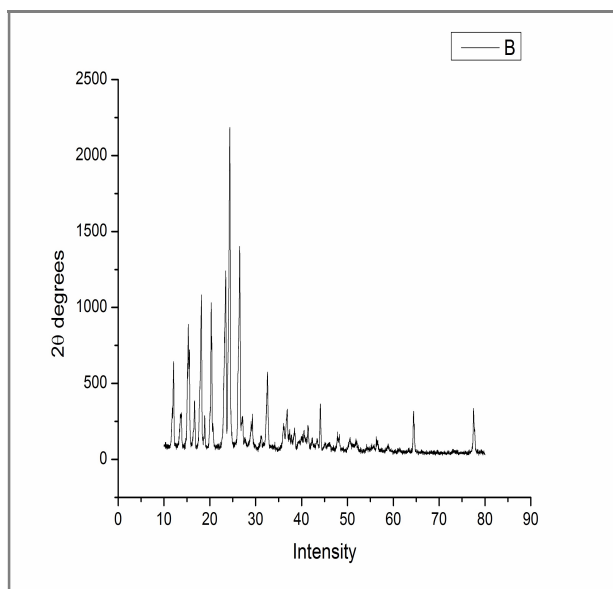
Fig 3. FTIR spectra of A) TMA and B) TMA loaded DPI.

DISCUSSIONS:

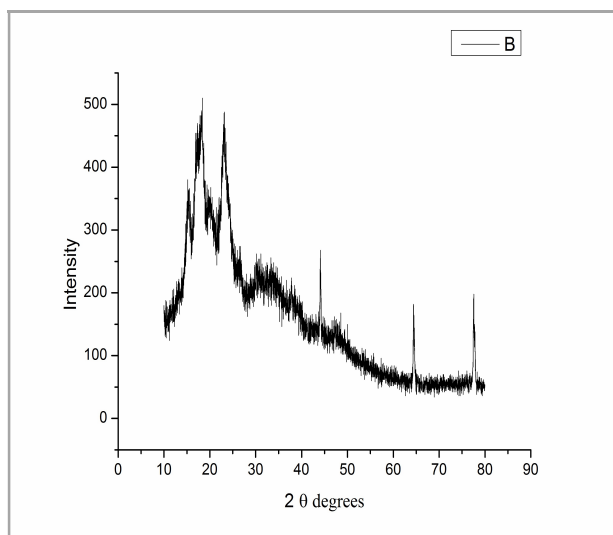
The present studies are the characterization of DPI and optimization batches of the microparticle. The spray dryer techniques were used for the preparation of DPI with a low concentration of organic solvent solution as compared to an aqueous solution. The optimization of microparticle particle size was determined by zeta size and particle size range shown in Table 1. The best microparticle particle formulation F1 possessed particle size of 0.55 μm and DPI formulation particle size range 0.222 μm . This particle range is suitable for pulmonary delivery. The ideal particle size for pulmonary delivery particle size range is 0-5 μm [28]. The flow properties of DPI were determined by the Tapped density, Carr's index, surface area and Hausner's ratio. The flow

property was found to be good. The drug content was 89 %. The surface morphology of TMA and DPI was determined by SEM instruments that showed the images and particles of TMA and DPI as depicted in Fig 4. The reported data SEM surface morphology and particles are spherical shape and free-flowing properties [20]. The X-RPD analysis of TMA and DPI are particles present in many intensive peaks shown Fig 5 and the pattern of X-RPD of TMA and DPI was crystalline. The reported data X-RPD analysis of DPI [22]. The *in-vitro* release studies of TMA and DPI studies were performed by dissolution apparatus using Type II USP Basket and PBS pH 7.4. The release of TMA and DPI in 48 h. The 30 % release of TMA and 70 % release of TMA loaded DPI in 48 h showed in Fig 6. The *in-vitro* release studies follow the

Zero-order kinetics because of higher R^2 value i.e. 0.973 when compared with the Higuchi model, Hixson model, Korsmeyer Peppas model and First-order kinetics. The reported data was in-release studies of DPI performed in the 21 days [20].



(A)



(B)

Fig 5. X-RD analysis of A) TMA and B) TMA loaded DPI.

CONCLUSION:

The DPI successfully prepared by spray drying techniques used DPPC, poloxamer-188 and beta-cyclodextrins as an excipient. The primary DPI particle size, surface morphology was excellent for pulmonary delivery and release studies of DPI were a better release rate for pulmonary delivery. From the above

experimental study result it could be concluded that the optimized TMA-loaded DPI could be successfully therapeutically used for asthma and delivery through pulmonary delivery. The TMA was a corticosteroid drug used as an anti-inflammatory for pathological conditions like asthma.

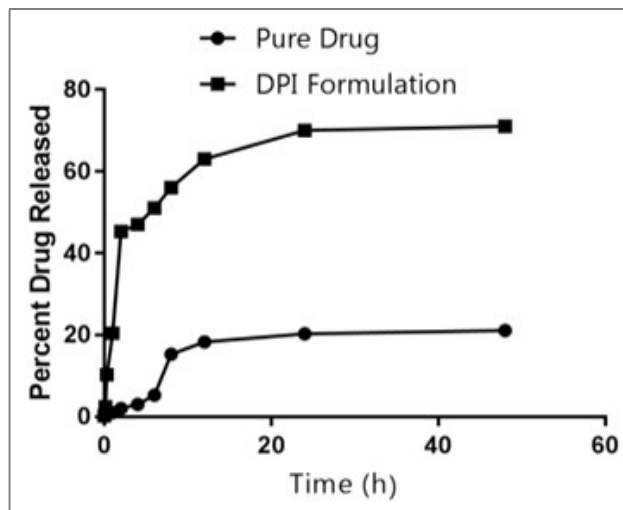


Fig 6. In-Vitro drug release profile of pure drug, TMA and TMA loaded DPI.

ACKNOWLEDGMENT:

Authors wish to thank ISF College of Pharmacy, Punjab, for providing the research facilities to complete this project work. The authors also wish to Thanks Sun Pharmaceutical for providing the sample drug Triamcinolone Acetonide.

REFERENCES:

1. Boulet LP, Fitzgerald JM, Reddel HK. The revised 2014 GINA strategy report: Opportunities for change. *Curr Opin Pulm Med*, 2015; 21(1): 1-7.
2. Zhang L, Han DM. An introduction of allergic rhinitis and its impact on asthma (ARIA) 2008 update. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*, 2008; 43(7): 552-527.
3. Allen DB, Bielory L, Derendorf H, Dluhy R, Colice GL, Szeffler SJ. Inhaled corticosteroids: Past lessons and future issues. *J Allergy Clin Immunol*, 2003; 112(3): 1-40.
4. Barnes PJ, Pedersen S. Efficacy and safety of inhaled corticosteroids in asthma. *Am Rev Respir Dis*, 1993; 148(4): S1-S26.
5. Crim C, Pierre LN, Daley-Yates PT. A review of the pharmacology and pharmacokinetics of inhaled fluticasone propionate and mometasone furoate. *Clin Ther*, 2001; 23(9): 1339-1354.

6. Beck-Broichsitter M, Gauss J, Packhaeuser CB, Lahnstein K, Schmehl T, Seeger W, *et al.* Pulmonary drug delivery with aerosolizable nanoparticles in an ex vivo lung model. *Int J Pharm*, 2009; 367(1–2): 169-178.
7. Hanania NA, Chapman KR, Kesten S. Adverse effects of inhaled corticosteroids. *Am J Med*, 1995; 98(2): 196-208.
8. Busse WW, Martin RJ, Szeffler SJ. Efficacy and safety overview of a new inhaled corticosteroid, QVAR (hydrofluoroalkane-beclomethasone extrafine inhalation aerosol), in asthma. *J Allergy Clin Immunol*, 2000; 106(6): 1209-1226.
9. Czock D, Keller F, Rasche FM, Häussler U. Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. *Clin Pharmacokinet*, 2005; 44(1): 61-98.
10. Hübner M, Hochhaus G, Derendorf H. Comparative pharmacology, bioavailability, pharmacokinetics, and pharmacodynamics of inhaled glucocorticosteroids. *Immunol Allergy Clin North Am*, 2005; 25(3): 469-488.
11. Rodrigo GJ. Advances in acute asthma. *Curr Opin Pulm Med*, 2015; 21(1): 22-26.
12. Sahib MN, Darwis Y, Peh KK, Abdulameer SA, Tan YTF. Rehydrated sterically stabilized phospholipid nanomicelles of budesonide for nebulization: physicochemical characterization and *in vitro*, *in vivo* evaluations. *Int J Nanomed*, 2011; 6: 2351-2366.
13. Berger WE, Bensch GW, Weinstein SF, Skoner DP, Prenner BM, Shekar T, *et al.* Bronchodilation with mometasone furoate/formoterol fumarate administered by metered-dose inhaler with and without a spacer in children with persistent asthma. *Pediatr Pulmonol*, 2014; 49(5): 441-450.
14. Chawes BL, Govoni M, Kreiner-Moller E, Vissing NH, Poorisrisak P, Mortensen L, *et al.* Systemic exposure to inhaled beclomethasone/formoterol DPI is age and body size dependent. *Respir Med*, 2014; 108(8): 1108-1116.
15. King RJ, Macbeth MC. Physicochemical properties of dipalmitoyl phosphatidylcholine after interaction with an apolipoprotein of pulmonary surfactant. *Biochim Biophys Acta*, 1979; 557(1): 86-101.
16. Carrier RL, Miller LA, Ahmed I. The utility of cyclodextrins for enhancing oral bioavailability. *J Control Release*, 2007; 123(2): 78-99.
17. Cosco D, Federico C, Maiuolo J, Bulotta S, Molinaro R, Paolino D, *et al.* Physicochemical features and transfection properties of chitosan/poloxamer 188/poly(D,L-lactide-co-glycolide) nanoplexes. *Int J Nanomed*, 2014; 9(1): 2359-2372.
18. Pearlman DS, Kane RE, Banerji D. Comparative dose-ranging study of triamcinolone acetonide inhalation aerosol using propellants hydrofluoroalkane 134a or P-12 in children with chronic asthma. *Curr Ther Res Clin Exp*, 1999; 60(11): 595-606.
19. Devrim B, Bozkiir A, Canefe K. Preparation and evaluation of poly(lactic-co-glycolic acid) microparticles as a carrier for pulmonary delivery of recombinant human interleukin-2: II. *In vitro* studies on aerodynamic properties of dry powder inhaler formulations. *Drug Dev Ind Pharm*, 2011; 37(11): 1376-1386.
20. Akhtar MS. A comprehensive review on fast dissolving tablets: A promising dosage forms. *J Pharm Adv Res*, 2019; 2(12): 733-740.
21. Kamble MS. Formulation & characterisation of chitosan based microspheres of Salbutamol sulphate dry powder inhaler formulation. *J Drug Deliv Ther*, 2012; 2(5): 37-41.
22. Zhao M, You Y, Ren Y, Zhang Y, Tang X. Formulation, characteristics and aerosolization performance of azithromycin DPI prepared by spray-drying. *Powder Technol*, 2008; 187(3): 214-221.
23. Gharse S, Fiegel J. Large Porous Hollow Particles: Lightweight Champions of Pulmonary Drug Delivery. *Curr Pharm Des*, 2016; 22(17): 2463-2469.
24. Panda M, Rao ME, Panda J, Patro J. Solid dispersion: An approach to enhance bioavailability. *J Pharm Adv Res*, 2021; 4(6): 1261-1276.
25. Li X, Vogt FG, Hayes D, Mansour HM. Design, characterization, and aerosol dispersion performance modeling of advanced spray-dried microparticulate/nanoparticulate mannitol powders for targeted pulmonary delivery as dry Powder inhalers. *J Aerosol Med Pulm Drug Deliv*, 2014; 27(2): 81-93.
26. Shetty N, Cipolla D, Park H, Zhou QT. Physical stability of dry powder inhaler formulations. *Expert Opin Drug Deliv*, 2020; 17(1): 77-96.
27. Rout PK, Nayak BS. Statistical evaluation of losartan microspheres prepared by w/o emulsion

- method using factorial design and response surface methodology. Asian J Pharm Clin Res, 2009; 2(4): 53-62.
28. El-Sherbiny IM, El-Baz NM, Yacoub MH. Inhaled nano- and microparticles for drug delivery. Glob Cardiol Sci Pract, 2015; 2015(1): 1-14.

Conflict of Interest: None

Source of Funding: Nil

Paper Citation: Jayaswal KN, Singh D*, Gupta GD. Formulation, Optimization, and Characterization of Spray-Dried Triamcinolone Acetonide Loaded Dry Powder Inhaler for Pulmonary Delivery. J Pharm Adv Res, 2021; 4(7): 1318-1326.