Budesonide- nanoparticles based inhaled therapy for potential treatment of COPD

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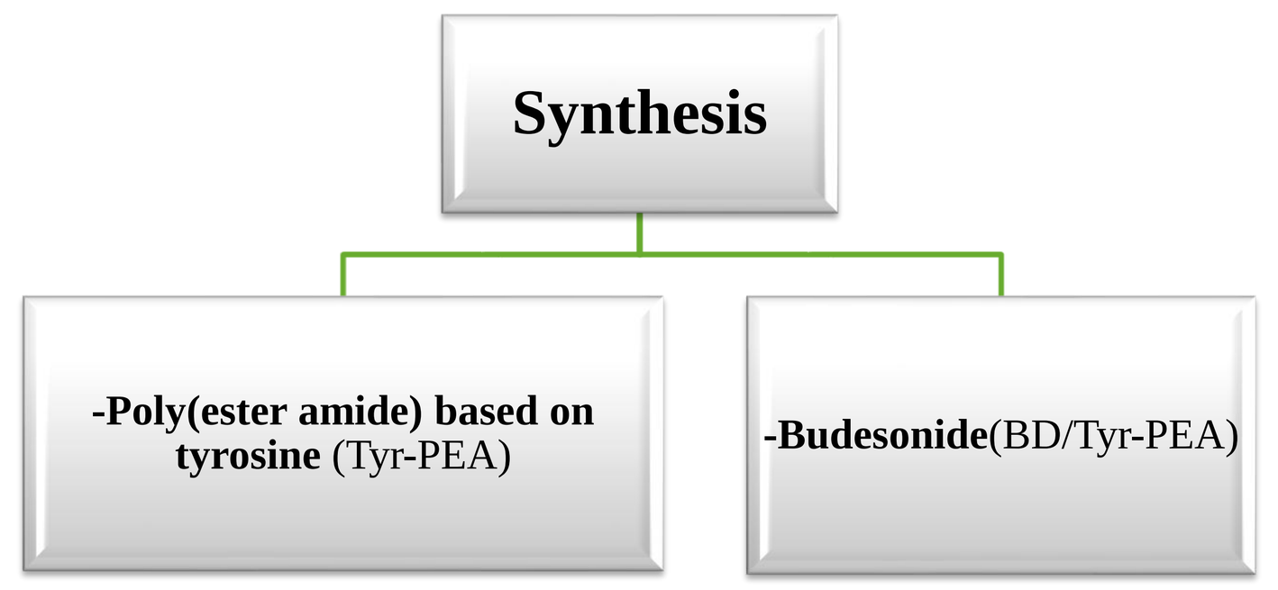
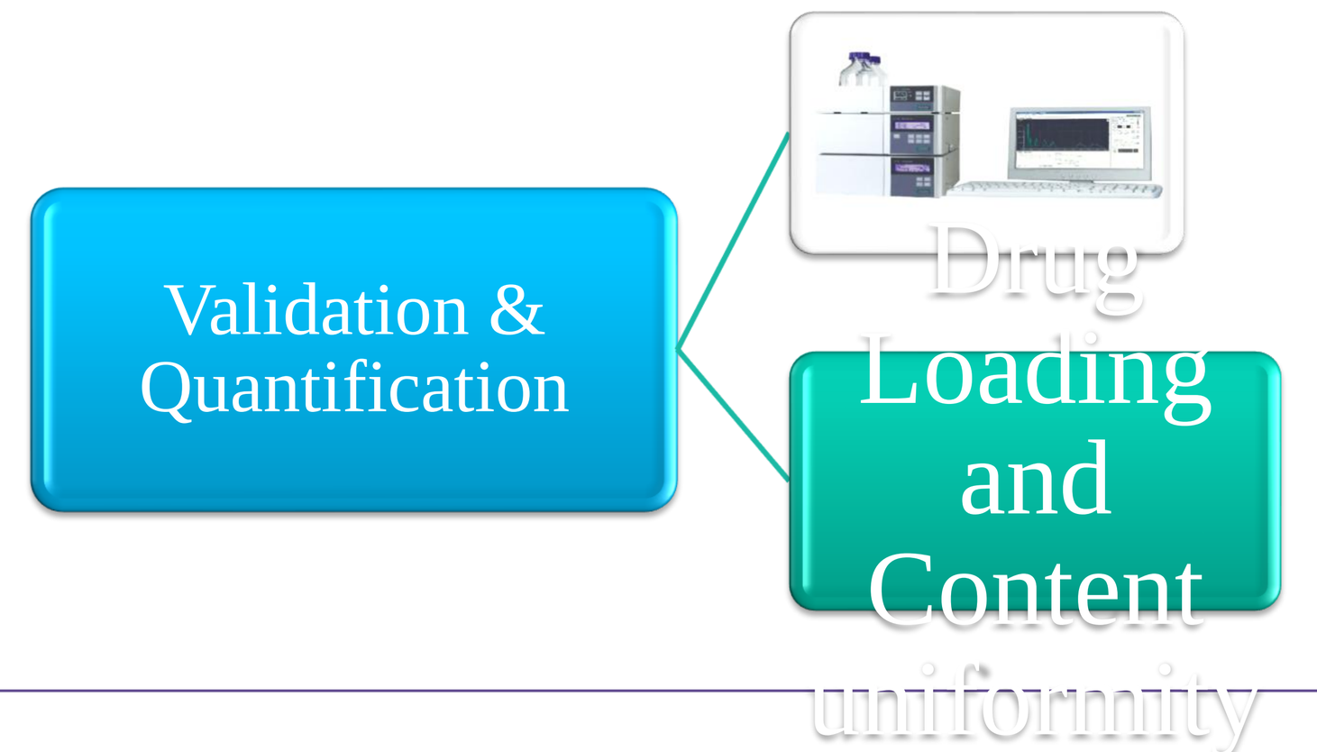
Introduction

- Polymers used in biomedicine are derived from natural origin or from biocompatible compounds such as (PLGA), (PGA) and (PLA).
- Poly (ester amide) s (PEAs) are a family of synthetic polymers whose structure includes both ester and amide linkages.
- In this study, we report the synthesis of PEAs derived from L-tyrosine. L-tyrosine is a naturally occurring amino acid that contains a phenolic hydroxyl group.
- Nanoparticles made with biodegradable polymers have been an important platform on which therapeutic molecules are coupled, functionalized, coated, or entrapped in different devices aimed to control the drug release into specific sites in the body.
- Dry powder inhaler (DPI) is a good option for budesonide for the treatment of COPD, it may help to overcome several limitations that are associated with other types of inhalation delivery systems (e.g., accuracy and reproducibility of the dose delivered, compliance and adherence issues, and environmental aspects).
- The present work focused on developing a novel biodegradable polymer synthesized of budesonide for the treatment of COPD.
- Due to the importance of this class of polymer in biomedical applications, it was worthwhile to investigate the use of this biodegradable polymer synthesized by interfacial polymerization with controlled surface functionality as a carrier in DPI for the pulmonary delivery of budesonide for the treatment of COPD.

Materials and Methods

- Budesonide, Fumaryl chloride, Methyl alcohol, Chloroform , Acetonitrile HPLC grade, Trifluoroacetic Acid (TFA) ,diethyl ether and Tyrosine. All chemicals were used as supplied without any further purification.





In *Vitro test* using NGI

Results

A: Synthesis

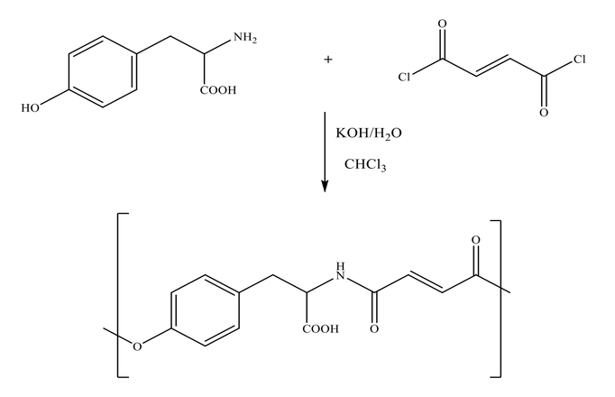


Figure 1. Synthesis of new PEAs based on tyrosine

Interfacial polymerization is used to create micro-nano capsules of BD drug. In interfacial polymerization, the two monomers and BD drug are dispersed in the organic and aqueous phases. The poly(ester amide) form was happening rapidly at the interface of the mini emulsions droplet by polycondensation mechanism and gave rise to the primary membrane.

B: Quantification and validation using HPLC analytical method

Table 1. Intermediate precision and reproducibility of HPLC method to evaluate inter and intraday reproducibility (mean± SD, n=3)

Budesonide Theoretical Concentration (µg/mL)	Intraday % Recovery (mean ± SD) (n=3)	Intraday %RSD (n=3)	Interday % Recovery (mean ± SD) (n=9)	Interday %RSD (n=9)
125	98.06 ± 3.73	3.80	96.89 ± 5.58	5.76
62.5	100.00 ± 5.45	5.45	99.82 ± 6.02	6.03
31.25	99.83 ± 6.28	6.29	100.40 ± 7.00	6.97
15.625	100.55 ± 7.48	7.44	101.14 ± 7.97	7.89
7.8125	99.40 ± 10.16			

C: Characterization of Tyr-PEA and BD/Tyr-PEA

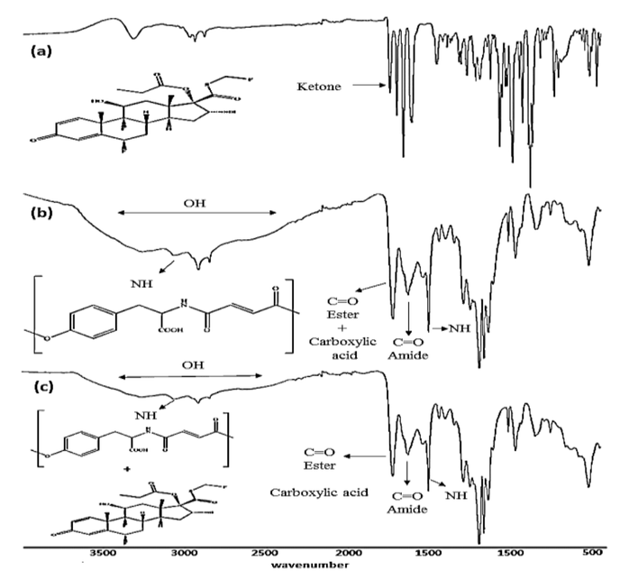


Figure 4. FTIR spectra of (a) BD, (b) (Tyr-PEA) and, (c) (FP/Tyr-PEA) NPs

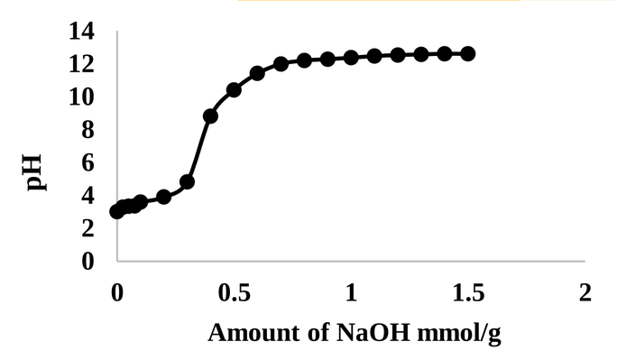


Figure 2. Titration curve of poly(ester amide)

Parameter \ Material	BD	Tyr-PEA	FP/ Tyr-PEA NP
Particle size (nm)	2107.2 ± 278.2	154.25 ± 22.5	167.5 ± 54.3
Polydispersity index	0.99 ± 0.18	0.41 ± 0.18	0.39 ± 0.11
Zeta potential (mV)	-18.5 ± 0.87	-31.93 ± 2.46	-31.43 ± 1.72

Table 2. Summary of particle size of BD, Tyrosine Poly(ester-amide) (Tyr-PEA) and Fluticasone propionate loaded Tyrosine Pol(ester amide) (FP/Tyr-PEA nanoparticles (NP) (mean ± SD, n=3)

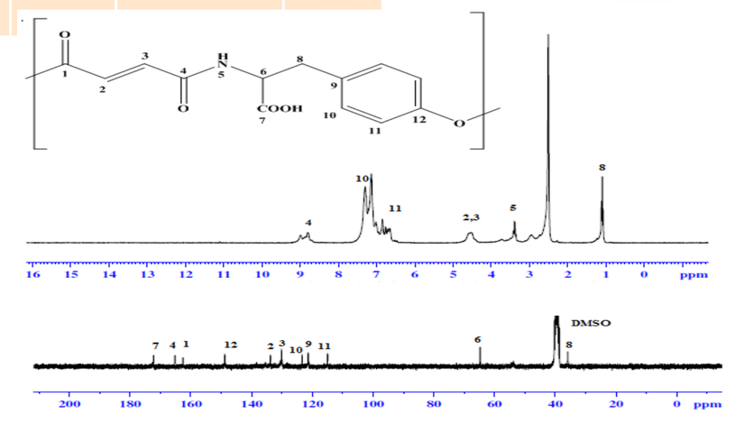
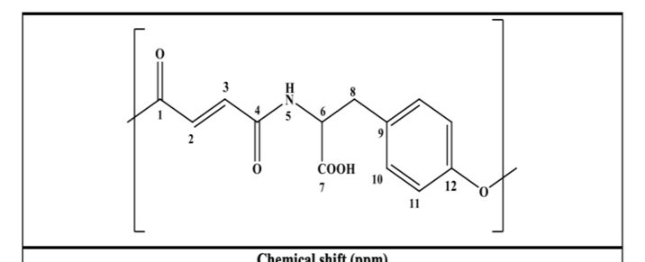


Figure 3. The ^{1}H NMR and ^{13}C NMR spectra



Chemical shift (ppm)	1	2	3	4	5	6	7	8	9	10	11	12
^{1}H	-	5.57	4.51	-	8.90	3.38	-	1.09	-	6.66-7.31		-
^{13}C	165.1	135.5	130.4	162.9	-	38.6	172.5	15.9	121.2	123.2	115.0	148.1

Figure 5. Structure of the polymer Confirmed by ^{13}C-NMR

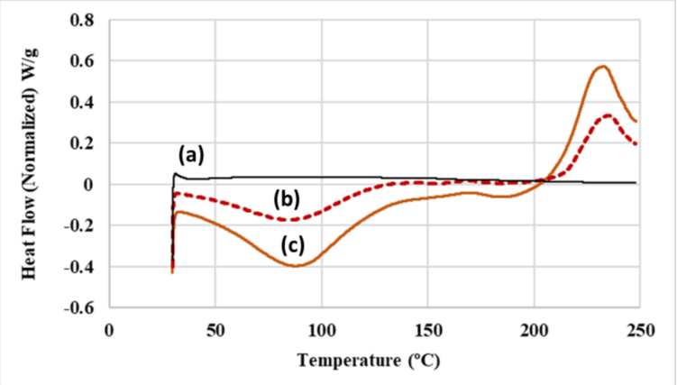


Figure 6. DSC profile of (a) BD, (b) poly(ester amide) based on tyrosine and (c) BD loaded poly(ester amide)

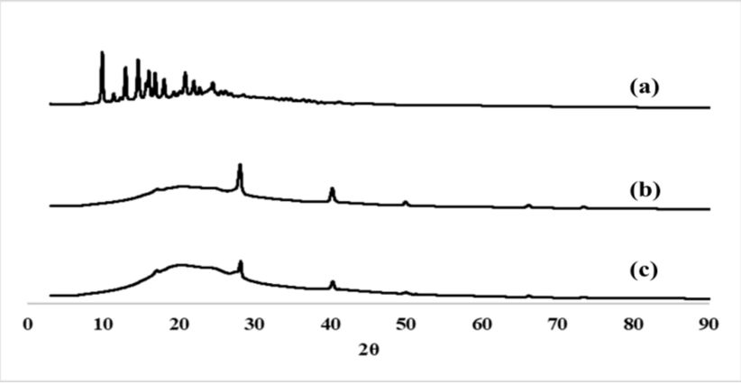


Figure 7. XRD curves of (a) BD, (b) Tyr-PEA (c) FP/Tyr-PEA

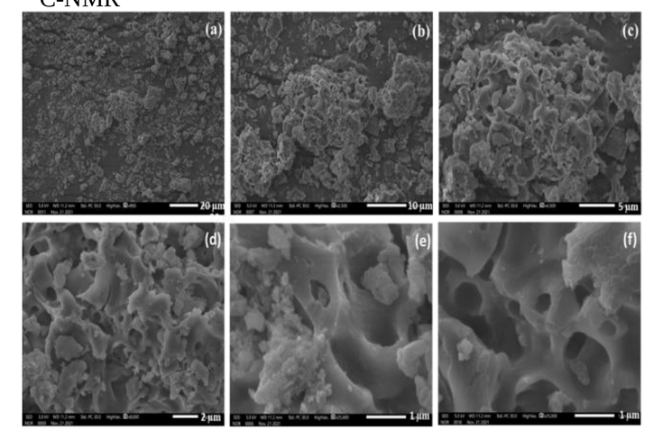


Figure 8. SEM images of BD loaded poly(ester amide) [fFP/Tyr-PEA]formula at various magnifications (a) 900 x, (b) 2,500 x, (c) 4,500 x, (d) 8,000 x, (e) 25,000 x, and (f) 25,000, highlighting porous aggregates

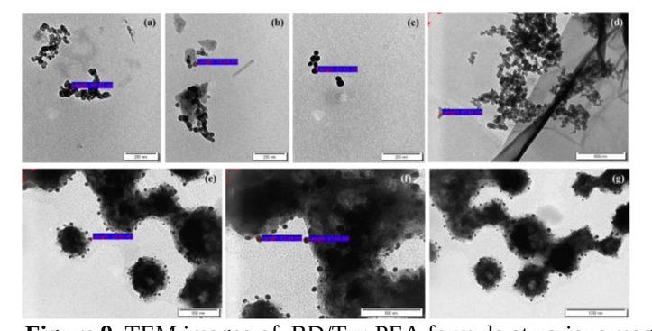
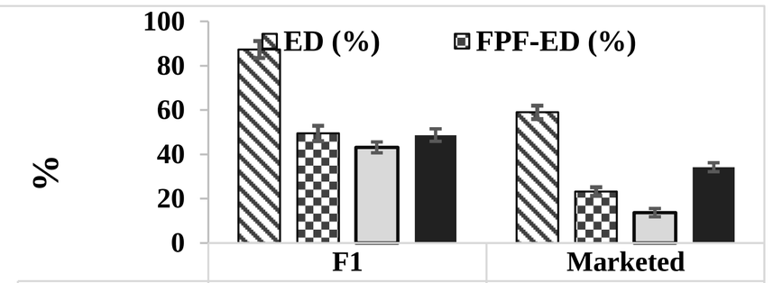


Figure 9. TEM images of BD/Tyr-PEA formula at various magnifications highlighting the presence of nanoaggregates

D: In-Vitro assessment of the formula (polymer contain BD) using NGI



	F1	Marketed
ED (%)	87.29	58.99
FPF-ED (%)	49.42	23.16
FPF-ND (%)	43.09	13.60
RD (ug)	48.63	34.15

Figure 10. Summary of in-vitro aerodynamic performance of BD using NGI. F1: each capsule contains 19 mg of the formula with BD content of 100 µg carried by polymer. Marketed: actuation contains 250 µg of BD. Results are presented as mean± SD, n=3. ED: %Emitted dose, FBD-ED: Fine Particle Fraction from Emitted Dose, FPF-ND: Fine Particle Fraction from Nominated Dose, RD: Respirable Dose

Table 2. MMAD and GSD of F1 and the Marketed product

Formulation	MMAD (µm)	GSD
F1	1.455	0.075
Marketed Product	1.434	0.074

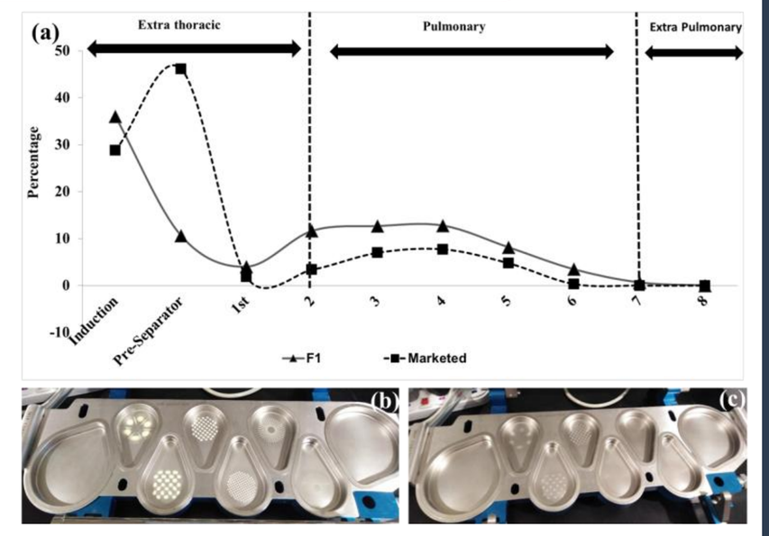


Figure 11. (a) *In vitro* comparison of aerodynamic particle size distribution of the F1 demonstrating the lung deposition of BD using NGI set at flow rate of 60l/min, **(b)** Deposition of the BD aggregates (F1) onto the NGI apparatus highlighting the powder on tray 1-7, **(c)** Deposition of the market product onto the NGI apparatus highlighting the white powder from tray 1-7

Conclusion

- BD-loaded-tyrosine based poly(ester amide) nanoaggregates were successfully prepared using interfacial polymerization technique.
- The optimized inhalable formulation has demonstrated favorable properties.
- Characterization techniques revealed the production of nanoaggregates capable of delivering a respirable dose of BD of 48.63 µg in comparison with 34.15 µg of the marketed product.
- The morphological analysis showed that the particles were spherical aggregates with primary size of 45.39 ± 6.32 nm.
- The employed interfacial polymerization technique based on amino acid enabled the production of a simple, cost-effective biodegradable and biocompatible alternative to the development of dry powder inhaler formulation.

References

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