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New complexes of inhaled Furosemide and Cyclodextrin:

Assessment of the bronchodilator effect

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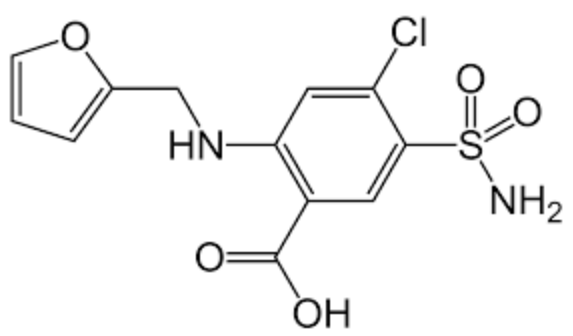
OUTLINE

- Introduction
- Methods
- Results
- Conclusions

Introduction

- Furosemide, a loop diuretic, is practically insoluble in water (0.01825 mg/mL) and is degraded by light[1,2].

- The bioavailability of orally administered furosemide in conventional dosage forms is poor and highly variable, and associated with low aqueous solubility, site-specific drug absorption, and first-pass metabolism[3].



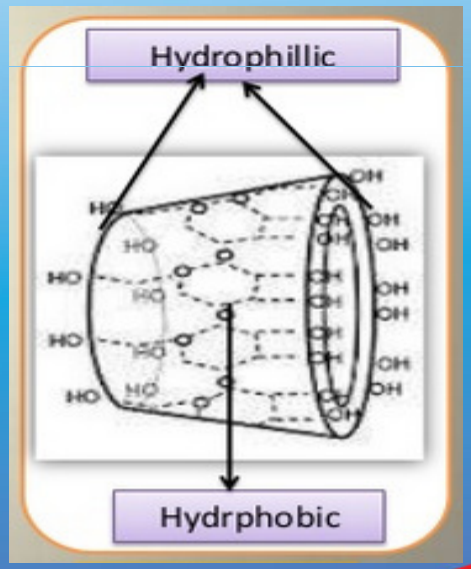
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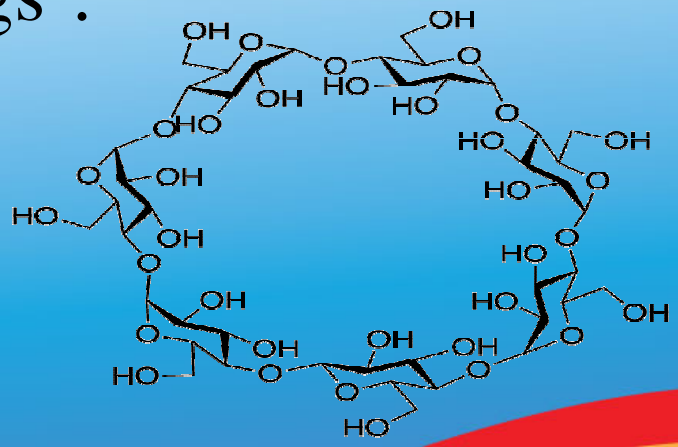
- Some studies showed that inhalation of furosemide alleviates dyspnoea by modulating vagal afferent activity in animal lung models[4] and reduces the intensity of induced dyspnoea in healthy individuals [5].

- Further studies suggested that nebulised furosemide might be effective against dyspnoea of asthma[6] and lung cancer [7].

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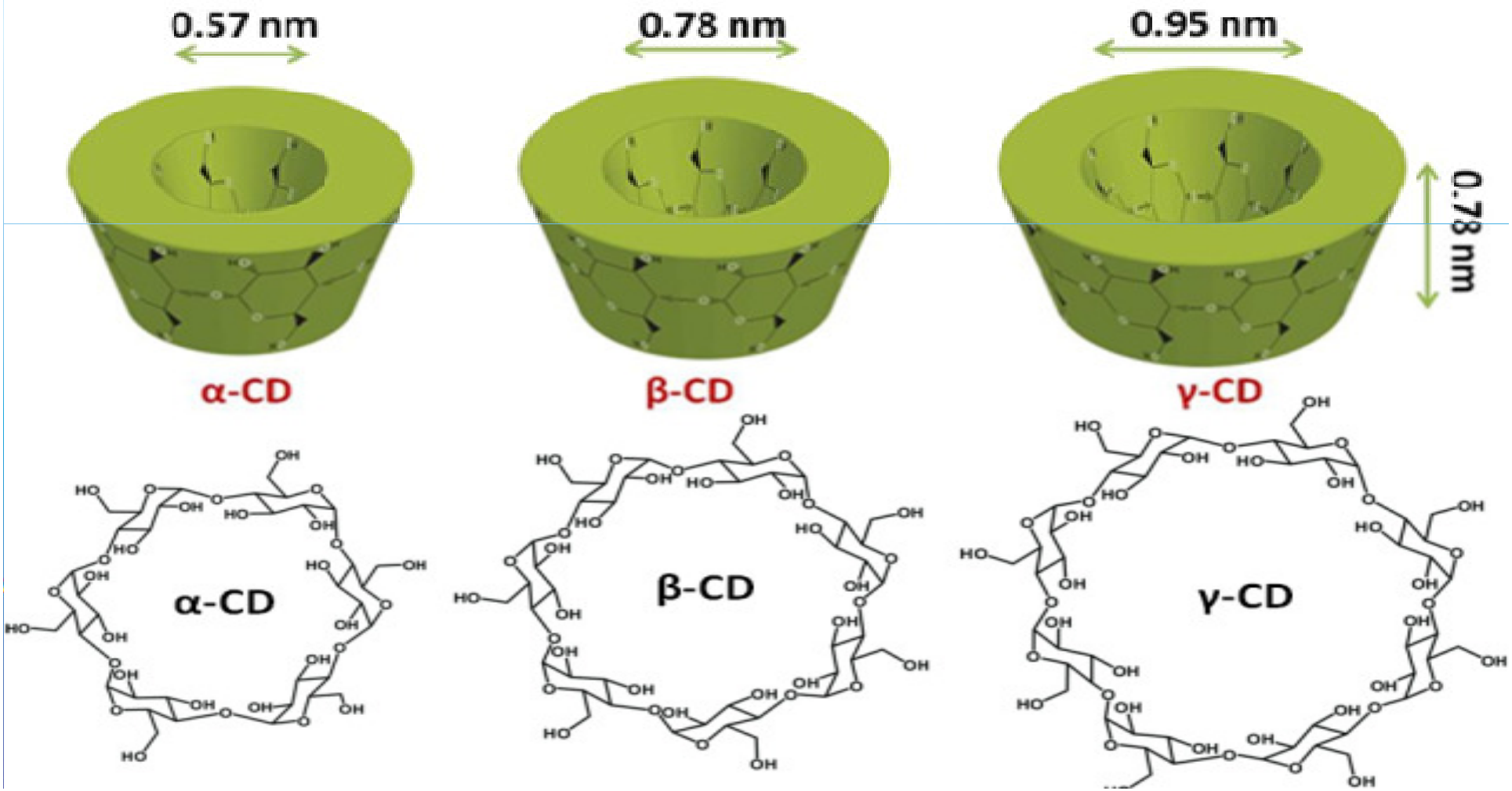
- β-cyclodextrin (β-CD) is a natural cyclic oligosaccharide and several studies have reported a positive effect of CD complexation on the physicochemical characteristics of many hydrophobic drugs[8].



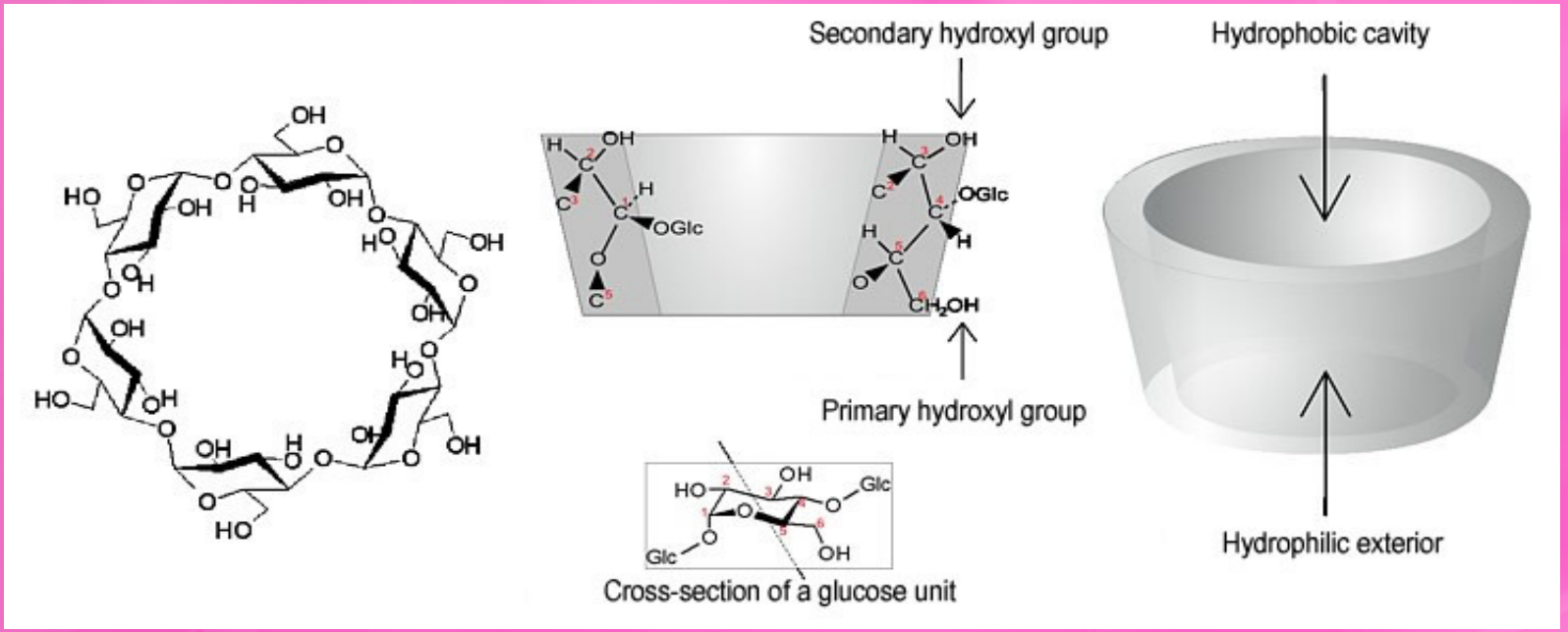


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Cyclodextrins contain 6, 7 or 8 dextrose molecules (α, β, γ-cyclodextrin) bound in a 1,4- configuration to form rings of various diameters.

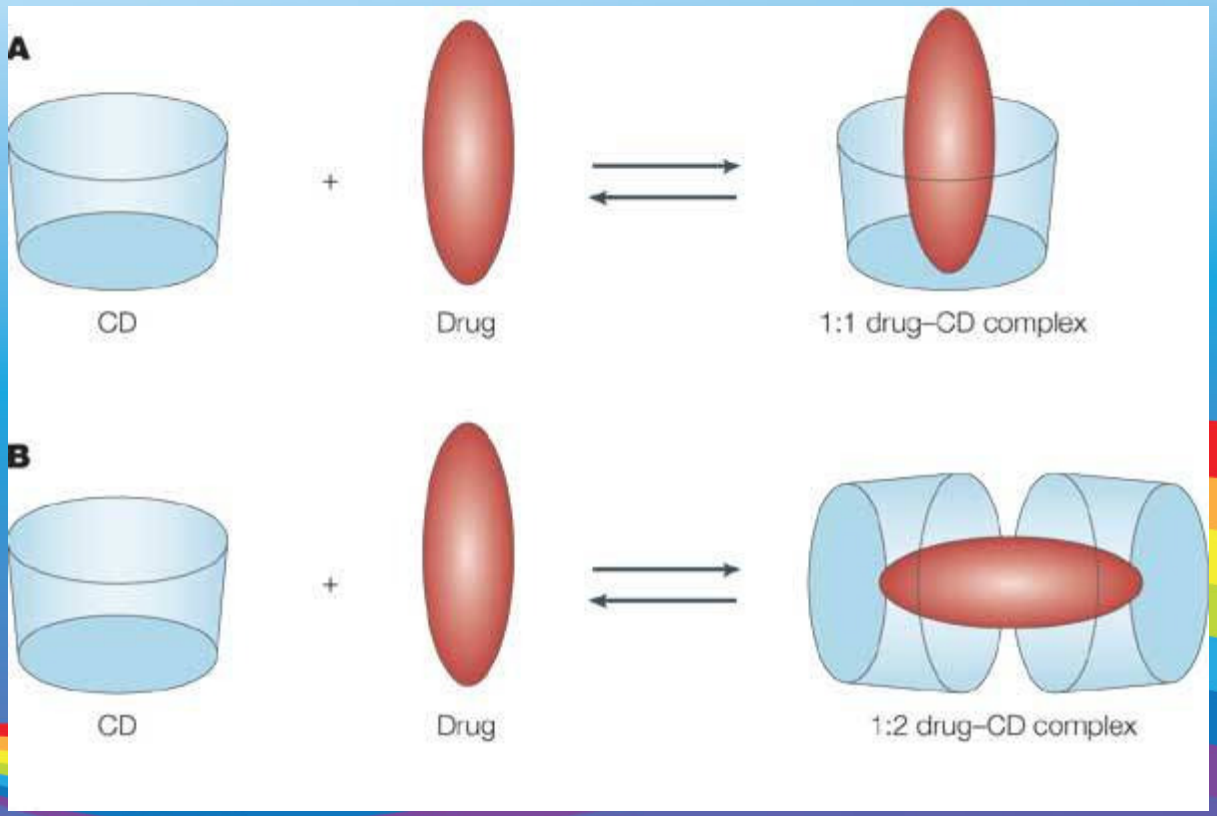


- The ring has a hydrophilic exterior and lipophilic core in which appropriately sized organic molecules can form non-covalent inclusion complexes.



- Complexation relies on relatively weak force such as **London forces**, **hydrogen bonding** and **hydrophobic interactions**.

- Inclusion complexation with agents such as β-cyclodextrin (β-CD) is one method to increase the aqueous solubility of a poorly water-soluble drug and thereby its stability and bioavailability[9].



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Aim of the Study

The objective of this study was to investigate the efficacy of nebulised furosemide administered singly or in combination with β-cyclodextrins (β-CDs) on asthma exacerbations in children .

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METHODS

Drugs

- The inclusion complexes of furosemide/β-CD in 1:1 and 1:0.5 molar ratios were prepared using the kneading technique, which is a simple, common and inexpensive method for preparing inclusion complexes.

THE KNEADING TECHNIQUE

THE INCLUSION COMPLEXES OF FUROSEMIDE B-CD PREPARATION

Furosemide
(330.74 mg)



β-CD
(1134.98 mg)



THE INCLUSION COMPLEXES OF FUROSEMIDE B-CD PREPARATION

Furosemide
(330.74 mg)

β-CD
(1134.98 mg)





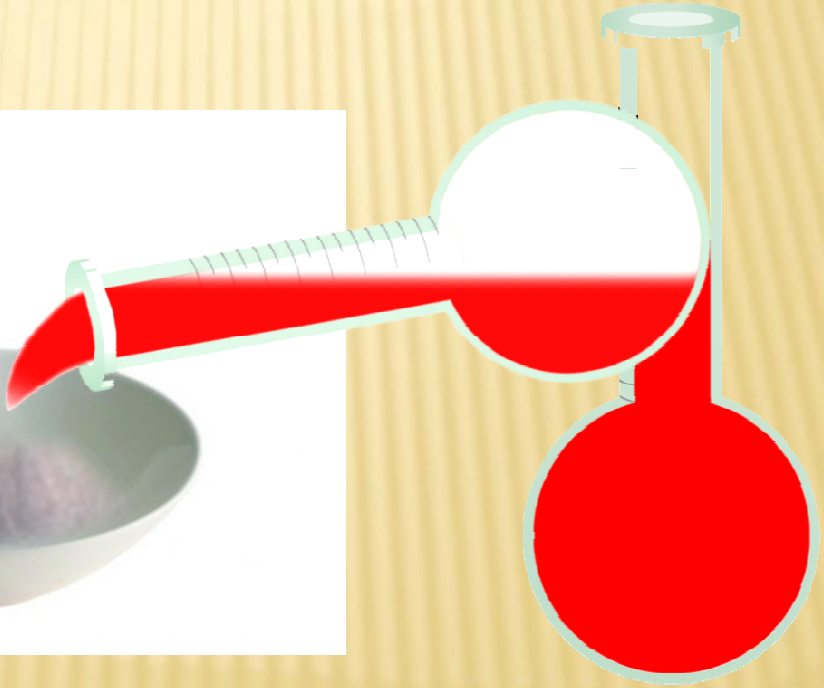


THE INCLUSION COMPLEXES OF FUROSEMIDE B-CD PREPARATION

Furosemide
(330.74 mg)

β-CD
(1134.98 mg)





4 mL Water–Ethanol Solution (50% v/v)

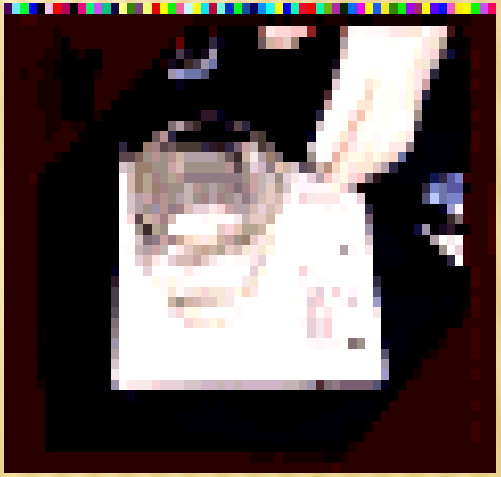
THE INCLUSION COMPLEXES OF FUROSEMIDE B-CD PREPARATION

Furosemide
(330.74 mg)

β-CD
(1134.98 mg)

15MIN KNEADING





4 mL Water–Ethanol Solution (50% v/v)

THE INCLUSION COMPLEXES OF FUROSEMIDE B-CD PREPARATION

Furosemide
(330.74 mg)

β-CD
(1134.98 mg)

THICK SLURRY



4 mL Water–Ethanol Solution (50% v/v)

THE INCLUSION COMPLEXES OF FUROSEMIDE B-CD PREPARATION

24 HOUR DRYING AT 50°C



OVEN

THE INCLUSION COMPLEXES OF FUROSEMIDE B-CD PREPARATION

POWDER



THE INCLUSION COMPLEXES OF FUROSEMIDE B-CD PREPARATION



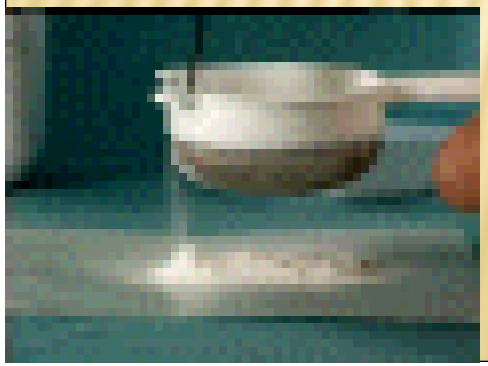
THE INCLUSION COMPLEXES OF FUROSEMIDE B-CD PREPARATION

FINAL POWDER



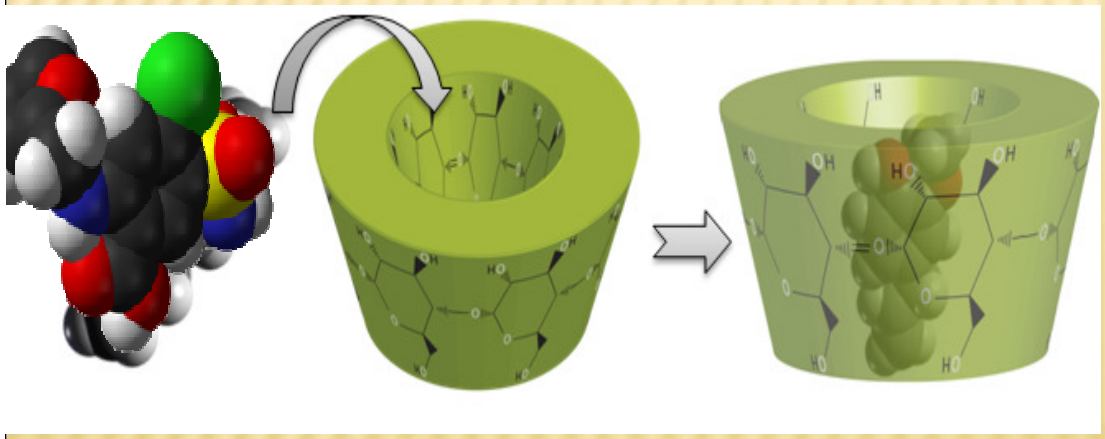


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THE INCLUSION COMPLEXES OF FUROSEMIDE B-CD PREPARATION

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STUDY DESIGN

The study was a single-blinded controlled randomised trial, involving five groups of children

Group 1	• 20 children received nebulised salbutamol (0.15 mg/kg)
Group 2	• 20 children received nebulised furosemide (1 mg/kg)
Group 3	• 20 children received nebulised salbutamol (0.15 mg/kg) plus nebulised furosemide (1 mg/kg)
Group 4	• 20 children received a complex of furosemide/β-CD in a 1:0.5 molar ratio
Group 5	• 20 children received a mixture of furosemide/β-CD in a 1:1 molar ratio

All drugs were dissolved in 4 mL normal saline before use in the nebulisation chamber.

Nebulisation was continued for 20 min until the nebulisation chamber was empty.

Pulmonary function was assessed by measuring:

(**FEV1**) forced expiratory volume in 1 s; (**FVC**) forced vital capacity; (**PFER**) peak expiratory flow rate; (**RR**) respiratory rate; (**SaO_2**) arterial oxygen saturation

in each patient before and 30 min after medication.

RESULTS AND DISCUSSION



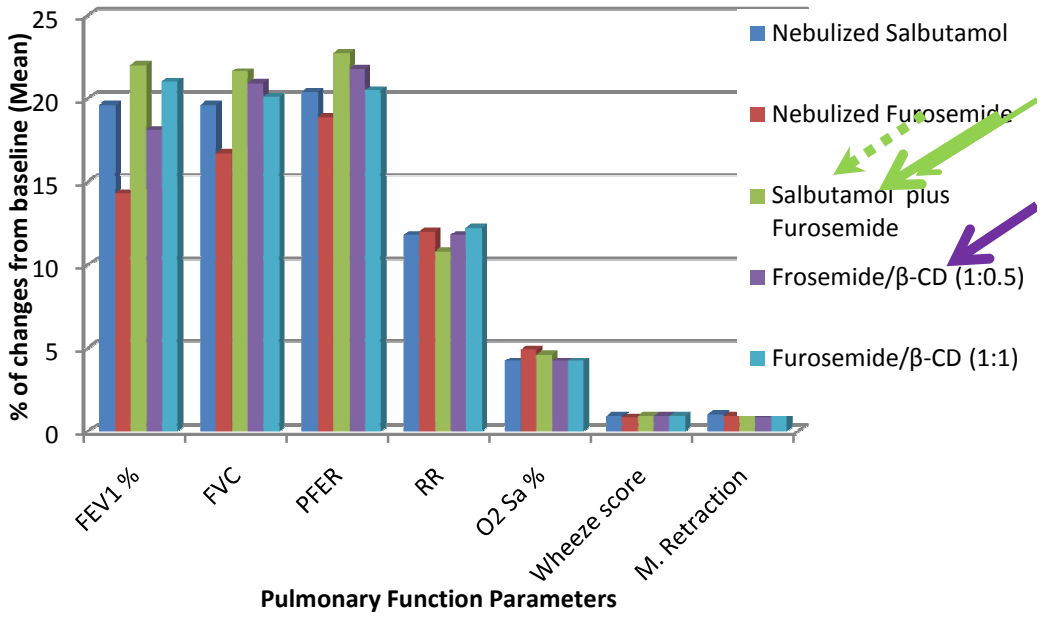
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Table Clinical outcomes before and after treatment in the five studied groups

Group	Group 1 Nebulised salbutamol			Group 2 Nebulised furosemide			Group 3 Salbutamol plus furosemide		
Time	0	30 min	p Value	0	30 min	p Value	0	30 min	p Value
FEV_1 (% of predicted value)	57.6±16.7	77.20±15.3	0.01	57.9±16.7	72.20±17.9	0.01	57.2±16.7	79.20±15.7	0.01
FVC (% of predicted value)	58.3±16.2	77.90±15.3	0.01	57.5±16.2	74.20±16.9	0.01	56.8±13.7	78.40±14.3	0.01
PFER (% of predicted value)	58.8±16.8	79.20±15.6	0.01	59.3±17.9	78.20±15.1	0.01	58.5±17.3	81.20±17.6	0.01
RR (breaths/min)	40.1±6.9	28.30±7.2	0.01	41.3±7.3	29.30±7.5	0.01	39.1±6.7	28.30±7.2	0.01
SaO_2, %	92.1±3.5	96.30±4.1	0.01	91.0±3.7	95.90±4.4	0.01	92.2±3.8	96.80±4.5	0.01
Wheeze score	2.5±0.8	1.60±0.4	0.01	2.7±0.7	1.90±0.6	0.01	2.6±0.7	1.7±0.3	0.01
Retraction	2.1±0.8	1.10±0.4	0.01	2.3±0.7	1.40±0.6	0.01	2.2±0.7	1.1±0.3	0.01

Values are mean±SD.
β-CD, β-cyclodextrin; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PFER, peak expiratory flow rate; RR, respiratory rate; SaO_2, arterial oxygen satur

Group 4 Furosemide/β-CD (1:0.5)			Group 5 Furosemide/β-CD (1:1)		
0	30 min	p Value	0	30 min	p Value
58.1±16.7	76.20±16.3	≤0.01	57.2±16.7	78.20±15.8	≤0.01
56.9±15.7	77.80±15.6	0.01	57.8±16.7	77.90±16.3	0.01
57.5±17.8	79.30±17.9	0.01	59.7±17.1	80.20±18.1	0.01
40.1±6.9	28.30±7.8	0.01	41.5±6.9	29.30±7.1	0.01
91.1±3.7	95.30±4.4	0.01	91.6±3.9	95.80±4.8	0.01
2.7±01	1.8±0.4	0.01	2.6±0.8	1.7±0.5	0.01
2.1±01	1.3±0.4	0.01	2.3±0.8	1.4±0.5	0.01



CONCLUSIONS

- Complexes of furosemide and CD improve FEV1, FVC, peak flow rate, SaO_2 and clinical scores significantly as compared to salbutamol or furosemide alone. The complex effect was nearly equal to the effect of the furosemide and salbutamol combination.

- These results suggest that CDs are promising solubility enhancers for improving the efficacy of poorly water-soluble drugs administered by inhalation.

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Many Thanks For Your Attention





Table 1 shows the age and gender of the patients in the different groups;

Table 2 Modified Becker's pulmonary index score

Score	Breathing rate/min	Presence of wheezing	Retraction
0	<30	–	–
1	30–40	End expiratory	Intercostal/subcostal
2	41–50	Throughout expiration	Intercostal+subcostal
3	>50	Throughout inspiration and expiration	Intercostal+subcostal +cervical

Table 1 Patient characteristics

	Group 1 n=20	Group 2 n=20	Group 3 n=20	Group 4 n=20	Group 5 n=20	p Value
Age (years)	11.6±3.0	10.4±2.3	12.4±2.3	11.7±2.3	12.4±2.3	0.9699
Gender (male/female)	11/9	13/7	11/9	15/5	12/8	0.2734

Values are mean±SD.

Patients

Children were diagnosed as having asthma according to the American Thoracic Society criteria.

Their characteristics are given in table 1.

The inclusion criteria were:

- Mild or moderate asthma exacerbation with a clinical asthma
- score (CAS) of between 1 and 6.
- Age between 6 and 18 years.
- Ability to perform a peak flow meter test.

- Pulmonary function was assessed by measuring **forced vital capacity** (FVC) and **forced expiratory volume in 1 s** (FEV1) with a computerised wedge spirometer in each patient before and 30 min after medication.

- **Flow rates** were measured using a Mini Wright peak flow meter.

- Furosemide may interfere with the transport of ions such as Na+, Cl– and K+ via the mucous epithelium, changing the osmolality of secretions and simultaneously modifying bronchial reactivity. Thus furosemide may have a relaxing effect on smooth muscles.

- Another explanation is that furosemide may reduce airway resistance and improve pulmonary distensibility by blocking the release of secondary constrictor mediators such as histamine or leukotrienes, leading to an increase in the exchange of gases.

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