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Taste masked formulation of montelukast sodium for the pediatric population and its evaluation

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ABSTRACT

The purpose of this study was to mask the metallic taste of montelukast sodium by complexation with beta-cyclodextrin and to incorporate the drug in a dispersible tablet for the pediatric population. The kneading method was applied to form the complex. The drug-beta-cyclodextrin (1:1) ratio was optimized by applying human panel method for taste evaluation and One-way ANOVA for drug release. The complex was mixed with other excipients to form a dispersible tablet. Results from an evaluation by a panel of nine human volunteers demonstrated that the dispersible tablets with taste masking complex improved the taste significantly. In conclusion, beta-cyclodextrin can effectively mask the metallic taste of the active pharmaceutical ingredient and does not affect the drug release.

INTRODUCTION

Organoleptic characteristics of pharmaceutical products i.e. taste, odor and appearance are essential factors in assessing the patient's acceptability; out of these organoleptic characteristics, taste is an important parameter governing patient compliance**.** Administration of a drug orally having a bitter and obnoxious taste, with an acceptable level of palatability is a challenge to the pharmacist in the present world, especially in the pediatric and geriatric formulation. Taste masking in the present day pharmaceutical industry has become a potential tool to improve patient compliance and commercial success of the product [1].

Montelukast is a leukotriene receptor antagonist, approved for use in pediatric patients. Montelukast modifies the action of leukotrienes, which are the most potent bronchoconstrictor, by blocking cysteinyl leukotriene receptors. A systemic drug like montelukast can reach lower airways and improves the peripheral function which plays a crucial role in the evolution of asthma [2]. Cyclodextrins are cyclic oligosaccharides consisting of six α-cyclodextrin, seven β-cyclodextrin, eight γ-cyclodextrin or more glucopyranose units linked by α-(1,4) bonds. They are also known as cycloamyloses, cyclomaltoses, and schardinger dextrins. In the inclusion complex formation, the drug molecule (guest molecule) fits into the cavity of complexing agent (host molecule) forming a stable complex. The complex is capable of masking the bitter taste of the drug by both decreasing the amount of particles exposed to the taste buds and/or by decreasing the drug solubility on ingestion, both activities leading to a decreasing bitterness of the drug [3].

One of the most important characteristics of cyclodextrins is the formation of inclusion complexes with various organic and inorganic guest molecules. Upon inclusion complexation, the characteristic properties of the guest molecule inside the cyclodextrin cavities, such as solubility, chemical reactivity, electrochemical properties and spectral properties will be changed significantly. The stability of the inclusion complexes depends on the size and the polarity of the guest molecules, the nature of the medium, and the temperature. Cyclodextrin is advantageous because of low hygroscopicity, less toxicity and also high fluidity and excellent compatibility and compressibility of cyclodextrin complexes [4].

The purpose of the present study was to formulate and evaluate taste masked dispersible tablet of montelukast sodium to increase the palatability of the drug. In the present work, an attempt was made to mask the taste by complexation technique. Taste improvement of the drug by β-cyclodextrin was done by simple complexation approach using kneading method with various ratios.

MATERIALS AND METHODS

Materials

Montelukast sodium was obtained as gift sample from Glenmark Lab (Nashik, India). β-cyclodextrin, crospovidone XL,

kollidon, tween 80, and sodium lauryl sulphate were obtained as gift sample from BASF India Limited (Mumbai, India).

Methods

Preparation of inclusion complexes

The binary systems of montelukast sodium (MTLKNa) and β-cyclodextrin (βCD) were prepared by kneading method. MTLKNa and βCD in the proportion of 1:1 to 1:5 concentrations were mixed in a mortar for 1 h with a small quantity of methanol. Distilled water**:**methanol (3:2) was added intermittently and kneaded thoroughly with a pestle to get slurry-like consistency. The slurry was dried in a hot air oven at a temperature of 45°C for 24 h. Dried complex was sifted with sieve # 80 and stored in a desiccator until further use.

Montelukast sodium characterization

Solubility studies

The aqueous solubility of montelukast sodium was determined by adding an excess amount of drug into vials containing water. They were equilibrated for 24 h. The supernatants were filtered and analyzed on double beam spectrophotometer (UV-1800, Shimadzu Corporation, Japan). The procedure was repeated with methanol and ethanol.

Fourier Transform Infrared Spectrophotometric analysis (FTIR)

Fourier transform IR spectra were recorded on FT-IR-Alpha Bruker 1206 0280, Germany [5]. In this study, potassium bromide disc method was employed. The powdered sample was intimately mixed with dry powdered potassium bromide. The mixture was then compressed into a transparent disc under high pressure using special dies. The disc was placed in IR spectrophotometer using a sample holder and spectrum were scanned over wave number range of 4000-400 cm^{-1}.

Differential Scanning Calorimetry (DSC) Analysis

Mettler-star "e", Switzerland, instrument was used to perform differential scanning calorimetry (DSC) measurements using aluminium pans. Indium standard was used to calibrate the instrument. The sample was hermetically sealed in an aluminium pan and heated at a constant rate of 20°C/min, over a temperature range of 40-300°C. The inert atmosphere was maintained by purging nitrogen through cooling unit at the flow rate of 100 ml/min [6].

Calibration curve of montelukast sodium in methanol

10 mg of montelukast sodium was weighed accurately and transferred to 100 ml volumetric flask. The drug was dissolved in methanol and the volume was made up with methanol. This was the solution of MTLKNa (100 µg/ml). 10 ml of above solution was taken and diluted up to 100 ml with methanol to make the standard stock solution of the drug (10 µg/ml). The prepared stock solution was further diluted with methanol to get working solution of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, and 4.0 µg/ml of MTLKNa to construct Beer's law plot for the pure drug. The absorbance was measured at λ_{max} 283 nm, against methanol as blank. The standard graph was plotted by absorbance on Y-axis and taking the concentration of drug on X-axis in the concentration range of 4 µg. The absorbance of solutions was recorded at 283 nm by using the UV/Visible spectrophotometer.

Excipients authentication

The samples were observed for its colour, odour, and appearance. Melting points of βCD was determined by using capillary tube method. The readings were taken in triplicate and average was taken. The solubility of βCD determined at room temperature in distilled water. The excess amount was added in water. The supernatant was filtered and evaporated, the residue was weighed.

Characterization of inclusion complexes

Drug content

The amount of MTLKNa present in βCD complex was determined by dissolving complex equivalent to 10 mg of MTLKNa into 10 ml of methanol and after suitable dilution with methanol. UV absorbance was measured at 283 nm.

Release rate study at simulated salivary fluid

The release of the montelukast sodium from the drug-βCD complex was studied at the pH of mouth (simulated salivary fluid) pH 6.8, to determine the amount of the drug that would be released in the mouth during the administration of the formulation. The bitterness of the taste is related to the amount of drug released in the mouth, the plain drug was used as a control.

Drug:βCD complex was subjected to release rate study. The complex was accurately weighed (equivalent to 4 mg of drug) and added to 5 ml simulated salivary fluid (pH 6.8) placed in the test tube. Aliquot was withdrawn after an interval of 1 min. The sample was filtered through Whatman filter paper. The absorbance was measured at 283 nm. Drug concentration in the sample was determined from the standard curve of the drug in simulated salivary fluid (pH 6.8). The reported values of percent drug release are average values of two readings.

Release rate study at the gastric pH

The release rate of drug and Drug:βCD complex was studied in simulated gastric fluid and 0.1 N HCl. Drug:βCD complex was weighed accurately and subjected to release rate study using USP dissolution test apparatus II (Model: Dissolution 2000 Apparatus: Lab India). The pure drug was used as the control and subjected to release rate study. 5 ml of the aliquot were withdrawn at 10 min time interval as per requirement and replacement was made each

Table 1. : Dissolution conditions for drug:βCD

Dissolution Apparatus	USP Type II (Paddle)
Media	0.1 N HCl
Speed	50 RPM
Temperature	37±0.5°C
Media volume	900 ml
Identification	UV λ_{max}-283 nm

Table 2. : Selected prototype formula (MTLKNa:βCD complex)

Ingredients	Quantity of Ingredients (mg)			
	Formulations			
	F1	F2	F3	F4
Drug:βCD complex	8	8	8	8
Crospovidone	14	35	14	35
Sodium starch glycolate	14	14	56	56
Polyvinylpyrrolidone K30	14	14	14	14
Mannitol (Pearlitol)	10.5	10.5	10.5	10.5
Magnesium stearate	3.75	3.75	3.75	3.75
Aspartame	3.50	3.50	3.50	3.50
Micro-crystalline cellulose	115	83.75	90.75	79.75
Flavour	q.s	q.s	q.s	q.s
Total	200 mg	200 mg	200 mg	200 mg

Table 3. : Selected prototype formula (with plain drug)

Ingredients	Quantity
Montelukast sodium	**4 mg**
Crospovidone	35 mg
Sodium starch glycolate	56 mg
Polyvinylpyrrolidone K30	14 mg
Mannitol (Pearlitol)	10.5 mg
Magnesium stearate	3.75 mg
Aspartame	3.50 mg
Micro-crystalline cellulose	73 mg
Flavour	q.s
Total	200 mg

time with 5 ml of fresh dissolution medium. Each of the 5 ml samples was filtered through Whatman filter paper. The drug concentration in the sample was determined from the standard curve of the montelukast sodium in 0.1 N HCl (283 nm). The reported values of percent drug release are average values of two readings.

Taste evaluation of drug: βCD complex

The sample of each drug-resin complex was subjected to sensory evaluation. The evaluation was performed by a panel of nine members with respect to bitter taste

Formulation and development of dispersible tablet

Dispersible tablets were prepared by using drug:βCD complex (1:1 ratio). The weight of complex was taken equivalent to a dose of the drug. Four different types of dispersible tablets were formed using the different type of super-disintegrating agents by direct compression method using compression machine (Cadmach) by using oval shape punch of size 17. These super disintegrating agents were crospovidone and sodium starch glycolate. Formulations were coded as formulation F1, F2, F3, and F4 respectively (along with these super-disintegrants, diluents, sweeteners and binder were also used in different concentrations as per the requirement).

Selection of prototype formula

Evaluation of dispersible tablet of drug-βCD complex

Following parameters were evaluated for tablets [7],

Appearance

Ten tablets of the optimized formulation were taken to check any surface roughness in the tablet formulation.

Hardness

The hardness of tablets was determined using Monsanto hardness tester and the average values were calculated.

Friability

The friability of tablets was measured by Roche friabilator for 4 min at 25 rpm. Accurately weighed ten tablets and placed in Roche friabilator for 100 revolutions, then dedust the tablets and weighed.

Dispersion time

The tablet was added to 10 ml of water and time required for complete dispersion was measured. Three tablets from each formulation were randomly selected and dispersion time was measured.

Table 4. : Five point scale for taste evaluation

Taste Characteristics	Score
Pleasant	0
Tasteless	1
Slightly bitter	2
Moderately bitter	3
Intensely bitter	4

Weight variation test

To study weight variation twenty tablets of the formulation were weighed using a Mettler Toledo electronic balance and the test was performed according to the official method. Determined the standard deviation amongst individual weight of all tablets.

Wetting time

A piece of tissue paper (12 cm x 10.75 cm) folded twice was placed in a petri dish (10 cm diameter) containing 10 ml of water. Eosin, a water-soluble dye, was added to a petri dish. A tablet was carefully placed on the surface of the tissue paper and allowed to wet completely. The time required for water to reach the upper surface of the tablet was noted as wetting time.

Wetting volume

The tablet was placed in the center of the petri dish and distilled water was added dropwise on the tablet with the help of a pipette. The volume required to completely disintegrate the tablet was noted as the wetting volume.

Uniformity of dispersion

Two tablets were placed in 100 ml of water and stirred gently until completely dispersed. A smooth dispersion was obtained which passes through a sieve screen with a nominal mesh aperture of 710 µm (sieve # 22).

Release rate study of the formulations

The release rate study of the tablets in the 0.1 N HCl was carried out with the parameter given in the (Table 1) to determine the amount of drug that would be released in the stomach after administration of the tablet.

Taste evaluation of complex and dosage form

A single-blind study was designed for the taste masking test and disintegration time in the buccal cavity. Nine volunteers were

Table 5. : Preformulation factors of drug

Parameters	Result
Colour	White powder
Odour	Odourless
Solubility	Freely soluble in water, methylene chloride and alcohol (as per certificate of analysis)
Melting point (by capillary method)	137-140°C

Table 6. : Documented result (as per certificate of analysis)

Parameter	Result
Description	Almost white powder
Solubility	Freely soluble in water, in methylene chloride and in alcohol
HPLC identification	The retention time of the major Peak, as obtained in the (S)-enantiomer of montelukast content test of the sample solution, correspond to that of the montelukast peak in the system suitability solution.
Test for sodium	A dense white precipitate indicating the presence of sodium ions.
Water (% w/w, by KF determined on 0.300 g)	1.1 (not more than 2.0)

Table 7. : Absorbance concentration data for standard curves of montelukast sodium in different solvents

Conc. (µg/ml)	Water:Methanol	0.1 N HCl	Phosphate buffer pH 6.8	Simulated salivary fluid
5	0.077	0.115	0.098	0.318
10	0.152	0.264	0.194	0.262
15	0.248	0.340	0.295	0.357
20	0.323	0.451	0.385	0.474
25	0.419	0.555	0.495	0.583
30	0.495	0.681	0.597	0.597

Table 8. : Optical characteristic of calibration curve

Media	Regression equation	Correlation coefficient R	λ_{max} (nm)
Water:Methanol	Y=0.016x-0.010	0.998	283
Phosphate buffer pH 6.8	Y=0.019x-0.004	0.999	283
Simulated salivary fluid	Y=0.021x+0.049	0.999	283
0.1 N HCl	Y=0.017x+0.033	0.998	283

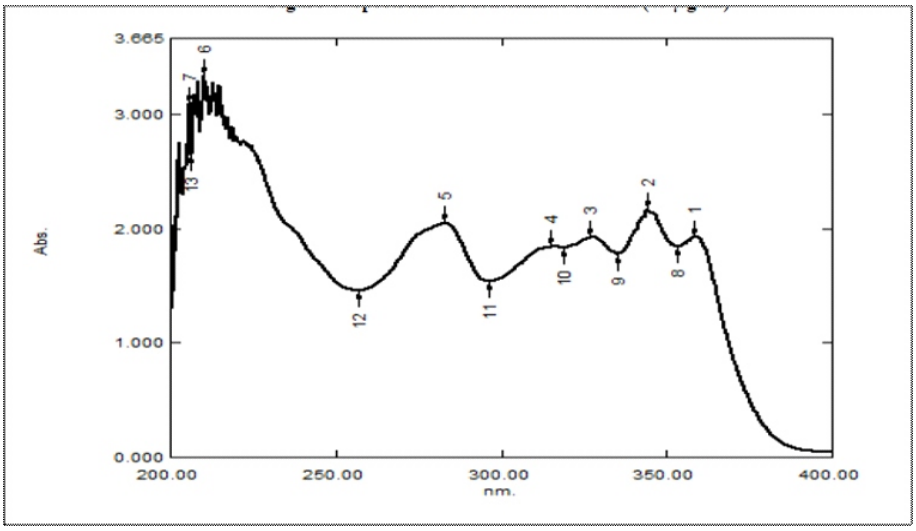

Fig 1. : UV spectrum of montelukast sodium in water:methanol (3:2)

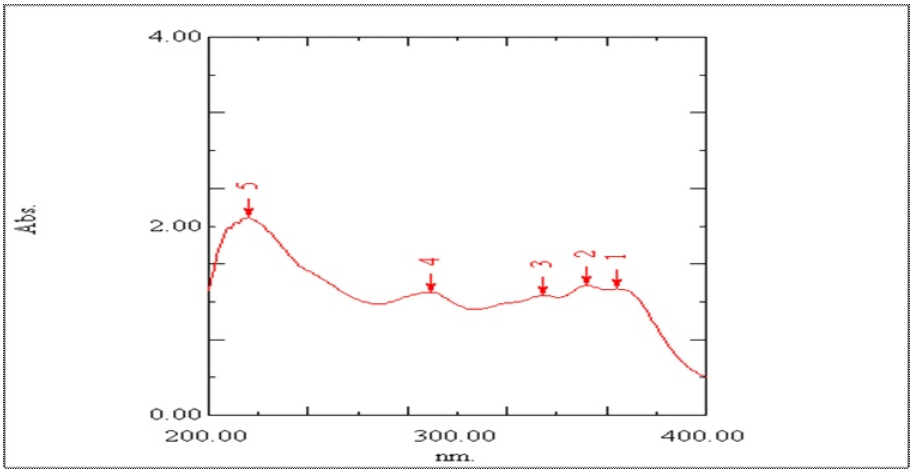

Fig 2. : UV spectrum of montelukast sodium in 0.1 N HCl

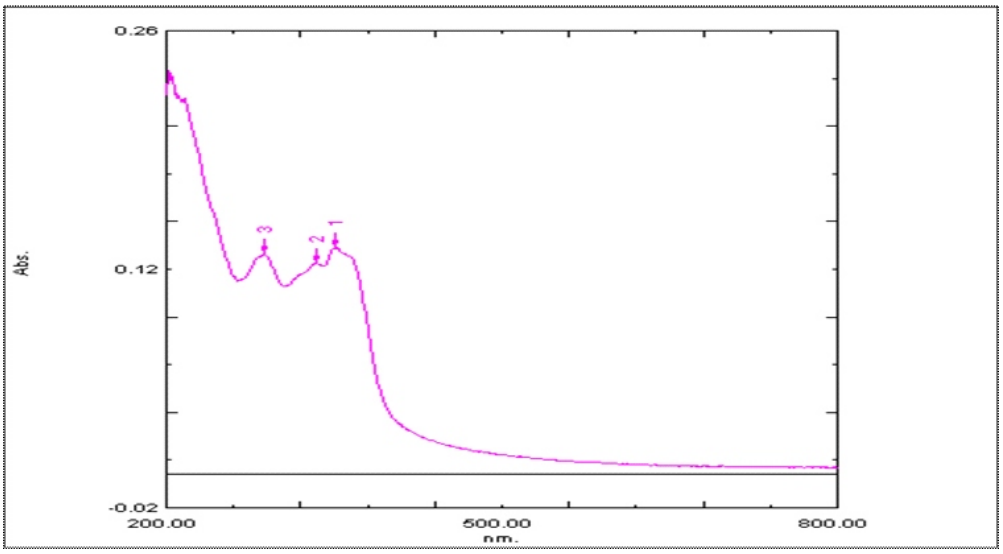

Fig 3. : UV spectrum of montelukast sodium in phosphate buffer

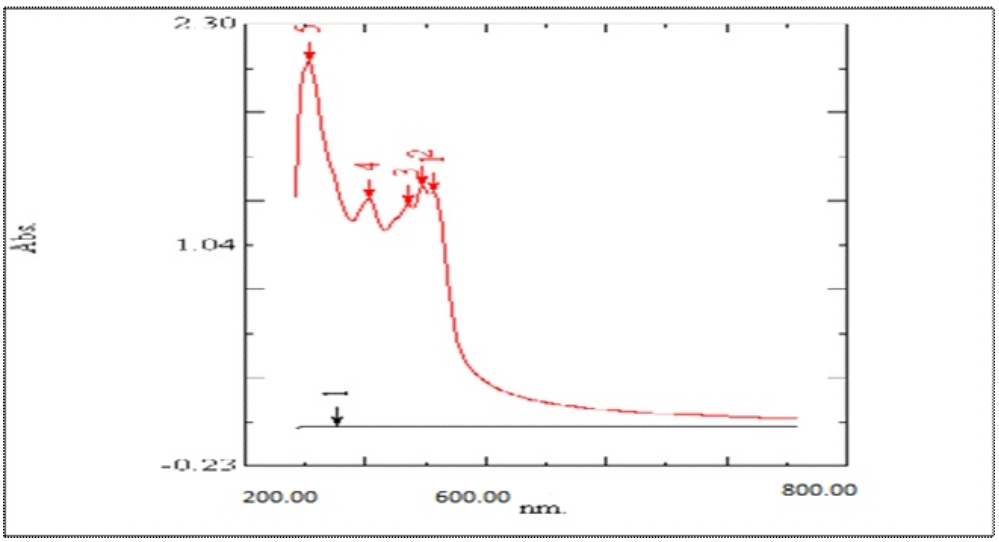

Fig 4. : UV spectrum of montelukast sodium in simulated salivary fluid

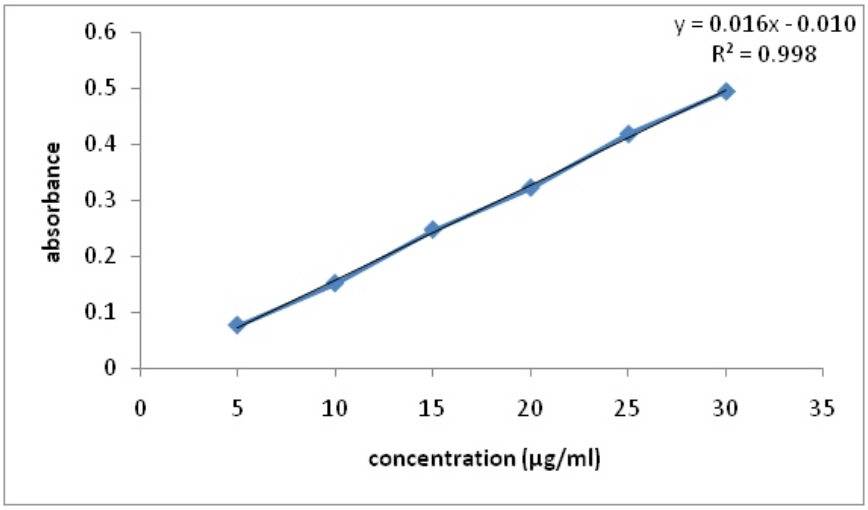

Fig 5. : Standard curve of montelukast sodium in water:methanol

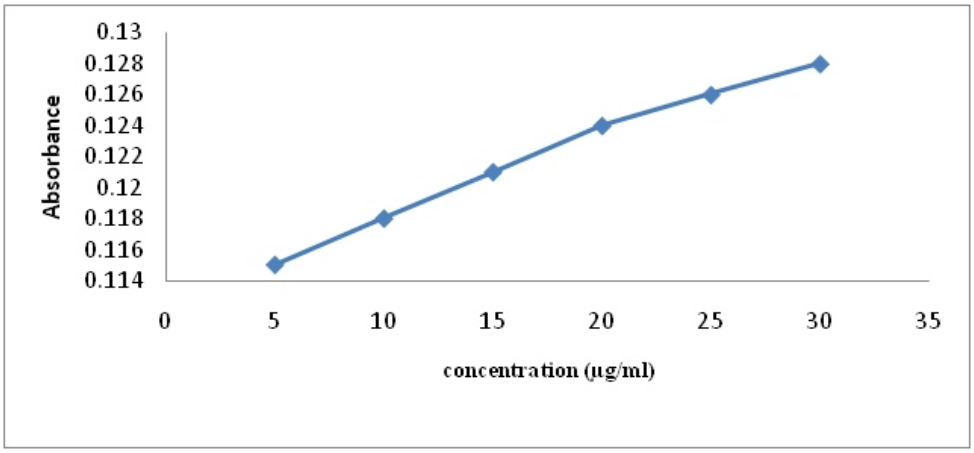

Fig 6. : Standard curve of montelukast sodium in 0.1 N HCl

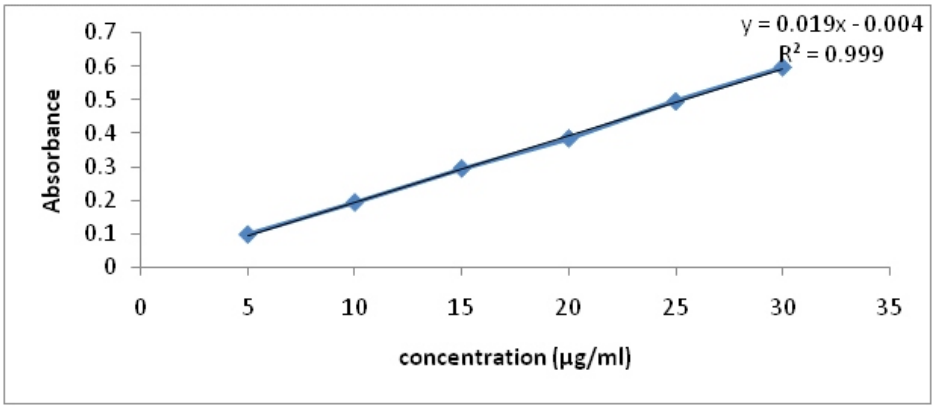

Fig 7. : UV spectrum of montelukast sodium in phosphate buffer

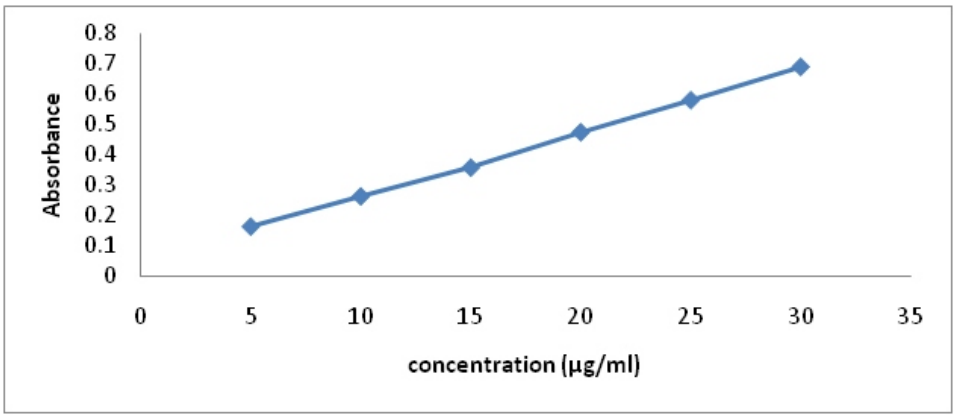

Fig 8. : Standard curve of montelukast sodium in simulated salivary fluid

asked to rate the bitter taste of the solid dispersions 1:0:5, 1:0.75, 1:1. The plain drug is used as a control. An approximate time for the tablet disintegration in the buccal cavity was also recorded.

RESULTS & DISCUSSION

Organoleptic analysis of Beta-cyclodextrin suggests a white colour with characteristic odour and slightly sweet taste. The melting point and solubility (in water) of βCD was found to be 259°C and 0.45 mg/ml respectively. Analysis of various preformulation factors of the drug are given in (Table 5) and results from certificate of analysis are given in (Table 6).

Absorbance concentration data for standard curves of montelukast sodium in different solvents are given in (Table 7) and optical characteristic of the calibration curve is shown in (Table 8). UV spectrum and standard curves of montelukast sodium in water:methanol, 0.1 N HCl, phosphate buffer and simulated salivary fluid are shown in (Figures 1-4) and (Figures 5-8) respectively.

The IR spectrum of montelukast exhibited a peak at 3366.88cm^{-1} due to N-H stretching and at 2923.68 cm^{-1} due to alkane saturated peak (Table 9). The IR spectrum of βCD showed

peaks at 3394 cm^{-1} and 2925.57 cm^{-1} (Figure 11). The IR spectrum of montelukast:βCD (1:1) inclusion complex prepared by kneading method has shown peaks at 3388.15 $cm^{-1}$and 2925.06 cm^{-1}. The shift in peaks indicates the interaction between montelukast and βCD.

The DSC thermogram of montelukast exhibited an endothermic peak at 69.81°C corresponding to its melting point (Figure 12). The DSC thermograms of montelukast: βCD (1:1) inclusion complex prepared by kneading method showed a slight shift in peaks which indicates an interaction between montelukast and βCD. The DSC thermograms of montelukast sodium and β-cyclodextrin individual samples as well as kneaded system in 1:1 ratio.

After evaluating the formulations on the parameter of hardness, thickness, friability, weight variation, dispersion time, wetting time, wetting volume, formulation F4 was selected as best formulation.

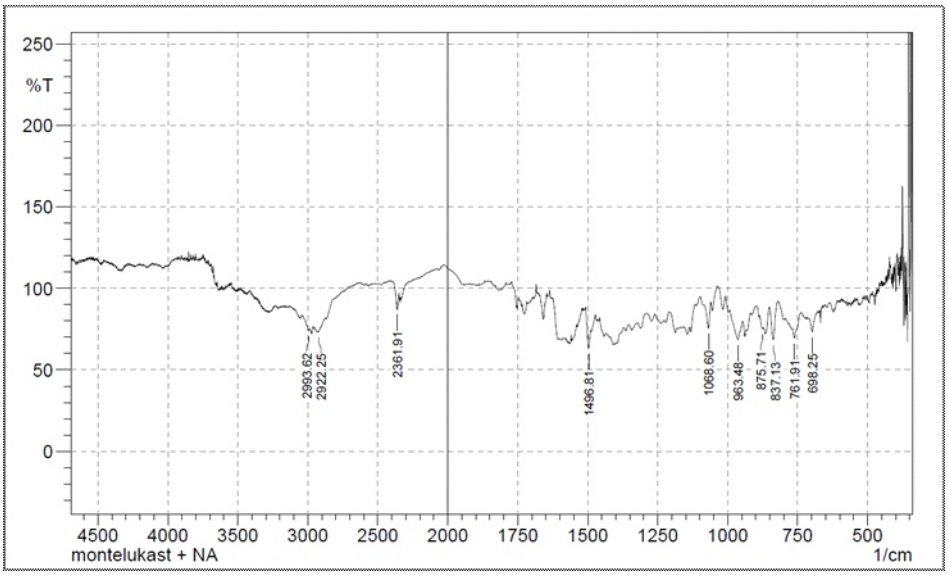

Fig 10. : Fourier transform infrared analysis of montelukast sodium

Table 9. : FTIR spectral analysis of montelukast sodium

IR signals(cm^{-1})	Assignment of functional groups
837.13	C-Cl stretch alkyl halide
1068.6	C-O stretch alcohol, carboxylic acid
1496.81	C-C stretch(in –ring aromatic)
2922.25	C-H stretch alkane
698.25	N-H wag pri, sec-amine

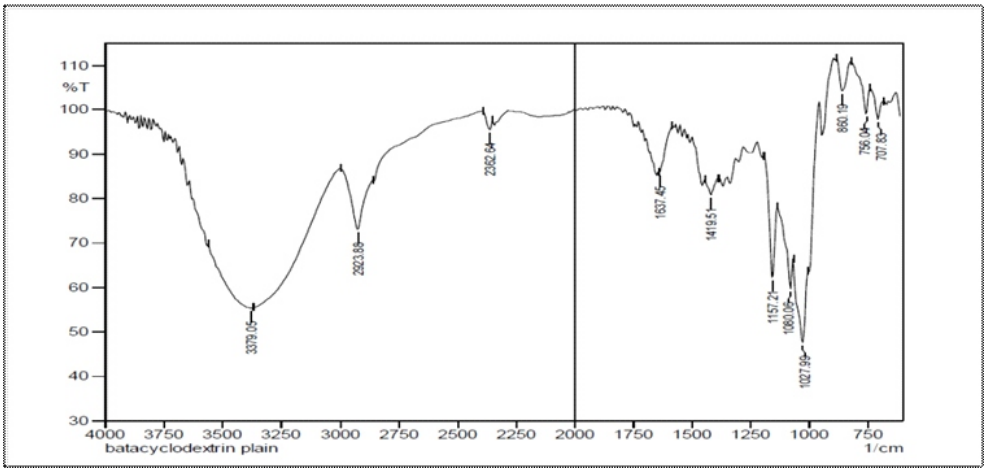

Fig 11. : FTIR spectrum of β-cyclodextrin

Table 10. : FTIR spectral analysis of βCD

Sr. No.	Peak observed (cm^{-1}) (βCD)	Interpretation
1	3379.05	O-H stretch
2	2923.88	C-H stretch
3	1637.45	C-H stretch
4	1419.51	C-O stretch
5	1157.21	C-O stretch
6	1027.99	C=O stretch

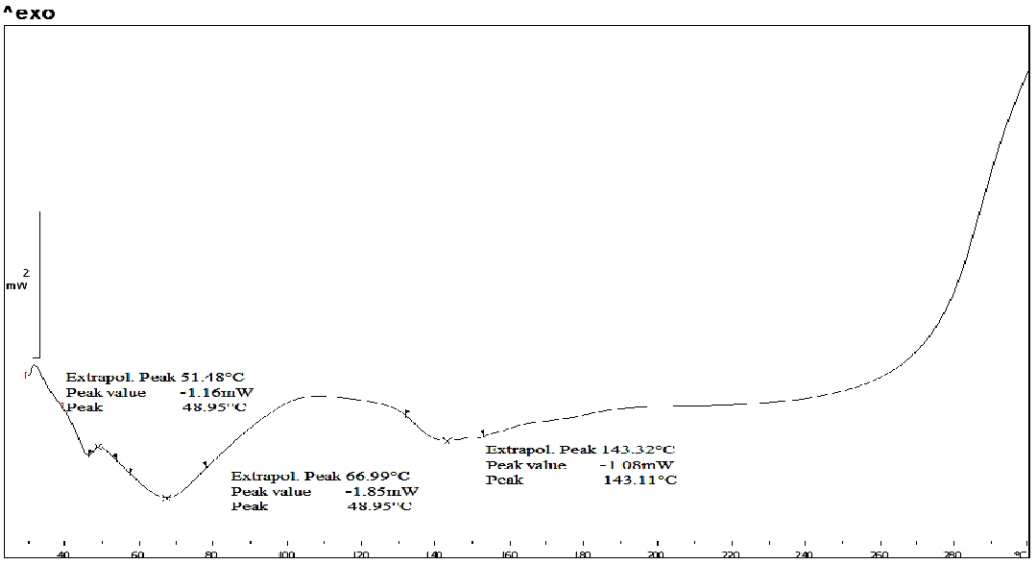

Fig 12. : DSC Thermogram of montelukast sodium

Table 11. : Drug content estimation of montelukast sodium in βCD complexes (kneading method)

Inclusion complex composition	Drug:βCD ratio	Code for complex	Percent drug content ±SD
Montelukast Na:βCD	1:0.5	C1	96.07± 0.33
	1.0.75	C2	98.16± 0.31
	1:1	C3	99.97± 0.22
	1:1.25	C4	99.97±0.21

Taste masking evaluation by human panel method:

Table 12. : Taste evaluation of solid drug:βCD complex

Ratio of Drug:βCD Complexes	Scores of drug-βCD complex									Average Bitterness value
	Group I			Group II			Group III			
	1	2	3	4	5	6	7	8	9	
Pure drug (C0)	4	4	4	4	4	4	4	4	4	4
1:0.5 (C1)	4	3	4	4	3	4	3	4	4	3.66
1:0.75 (C2)	3	2	3	3	2	3	3	3	3	2.77
1:1 (C3)	1	1	1	1	1	2	1	1	1	1.11
1:1.25 (C4)	1	1	1	2	1	1	1	1	1	1.11

Release rate study of complexes

Table 13. : Percent drug release of plain montelukast sodium in phosphate buffer pH 6.8

Ratio of Drug:βCD	Percent Drug Release in Phosphate Buffer pH 6.8 After 60 sec
Pure Drug (C0)	61.80 ± 0.0130
1:0.5 (C1)	10 ± 0.020
1:0.75 (C2)	4 ± 0.08
1:1 (C3)	1 ± 0.04
1:1.25 (C4)	1.03 ± 0.07

Table 14. : ***Statistical analysis:*** Data entered in (Table 13) is subjected to statistical analysis by One-way ANOVA and Dunnett's multiple comparison test

One-way ANOVA								
F				41830				
P value				< 0.0001				
P value summary				****				
Are differences among means are statistically significant? (P < 0.05)				Yes				
R Value				0.9999				
ANOVA table		SS	DF	MS	F (dFn, DFd)	P value		
Treatment (between columns)		8161	4	2040	F (4, 10) = 41830	P < 0.001		
Residual (within columns)		0.4877	10	0.04877				
Total		8161	14					
Number of Families		1						
Number of comparison per families		4						
Alpha	0.05							
Dunnett's multiple comparison test.	Mean Diff	95% CI of diff		Significant?		Summary		
C0 vs C1	51.80	51.28 to 52.32		Yes		****		
C0 vs C2	57.56	57.04 to 58.08		Yes		****		
C0 vs C3	60.80	60.28 to 61.32		Yes		****		
C0 vs C4	60.77	60.25 to 61.29		Yes		****		
Test Details	Mean 1	Mean 2	Mean Diff	SE of diff	n1	n2	q	DF
C0 vs C1	61.80	10.00	51.80	0.1803	3	3	287.3	10
C0 vs C2	61.80	4.240	57.56	0.1803	3	3	319.2	10
C0 vs C3	61.80	1.000	60.80	0.1803	3	3	337.2	10
C0 vs C4	61.80	1.030	60.77	0.1803	3	3	337.0	10

Table 15. : Percent drug release of plain MTLK-Na in simulated salivary fluid

Ratio of Drug:βCD	Percent drug release in phosphate buffer pH 6.8 After 60 sec
Pure Drug (C0)	61.43 ± 0.0110
1:0.5 (C1)	12 ± 0.020
1:0.75 (C2)	3 ± 0.08
1:1 (C3)	1 ± 0.02
1:1.25 (C4)	1.05± 0.04

Table 16. : ***Statistical analysis:*** Data entered in (Table 15) is subjected to statistical analysis by One-way ANOVA and Dunnett's multiple comparison test

One-way ANOVA					
F			1.129e +006		
P value			< 0.0001		
P value summary			****		
Are differences among means are statistically significant? (P < 0.05			Yes		
R Value			0.9999		
ANOVA table	SS	DF	MS	F (dFn, DFd)	P value
Treatment (between columns)	8091	4	2023	F (4, 10) = 1.129e +006	P < 0.0001
Residual (within columns)	0.01791	10	0.001791		
Total	8091	14			

Number of Families	1			
Number of comparison per families	4			
Alpha	0.05			
Dunnett's multiple comparison test.	Mean Diff	95% CI of diff	Significant?	Summary
C0 vs C1	49.43	49.33 to 49.53	Yes	****
C0 vs C2	58.43	58.33 to 58.53	Yes	****
C0 vs C3	60.43	60.33 to 60.53	Yes	****
C0 vs C4	60.38	60.28 to 60.48	Yes	****

Test Details	Mean 1	Mean 2	Mean Diff	SE of diff	n1	n2	q	DF
C0 vs C1	61.43	12.00	49.43	0.03456	3	3	1430	10
C0 vs C2	61.43	3.000	58.43	0.03456	3	3	1691	10
C0 vs C3	61.43	1.000	60.43	0.03456	3	3	1749	10
C0 vs C4	61.43	1.050	60.38	0.03456	3	3	1747	10

Table 17. : Percent cumulative release of montelukast sodium in 0.1 N HCl

Time (min)	Cumulative percent drug release
5	64.93±1.407
10	71.32 ±0.812
15	79.96 ±2.150
20	81.09 ±1.987
25	89.47 ±1.892
30	96.51± 1.99

Table 18. : Percent drug release of MTLKNa complex in 0.1N HCl (pH 1.2)

Time (min)	Percent cumulative release of montelukast sodium			
	1:0.5	1:0.75	1:1	1:1.25
5	31.90±2.125	35.19±1.409	41.20±0.435	42.31±0.321
10	41.76±0.812	45.04±1.235	51.05±0.764	53.35±0.664
15	57.71±1.407	59.12±1.762	65.98±0.654	61.73±0.224
20	76.01±1.765	77.42±1.985	83.65±0.657	79.61±0.327
25	81.64±1.654	84.92±1.627	90.12±0.325	89.09±0.245
30	95.72±2.436	94.12±0.301	96.86±0.654	96.89±0.321

Table 19. : ***Statistical analysis:*** Data entered in (Table 18) is subjected to statistical analysis by One-way ANOVA and Dunnett's multiple comparison test

One-way ANOVA								
F				1.058				
P value				0.4257				
P value summary				Ns				
Are differences among means are statistically significant? (P < 0.05				No				
R Value				0.2974				
ANOVA table		SS	DF	MS	F (dFn, DFd)		P value	
Treatment (between columns)		10.26	4	2.565	F (4, 10)= 1.058		P = 0.4257	
Residual (within columns)		24.24	10	2.424				
Total		34.50	14					
Number of Families		1						
Number of comparison per families		4						
Alpha	0.05							
Dunnett's multiple comparison test.	Mean Diff	95% CI of diff		Significant?		Summary		
C0 vs C1	0.7900	-2.884 to 4.464		No		Ns		
C0 vs C2	1.795	-1.879 to 5.469		No		Ns		
C0 vs C3	-0.3500	-4.024 to 3.324		No		Ns		
C0 vs C4	-0.3770	-4.051 to 3.297		No		Ns		
Test Details	Mean 1	Mean 2	Mean Diff	SE of diff	n1	n2	q	DF
C0 vs C1	96.51	95.72	0.7900	1.271	3	3	0.6215	10
C0 vs C2	96.51	94.72	1.795	1.271	3	3	1.412	10
C0 vs C3	96.51	96.86	-0.3500	1.271	3	3	0.2754	10
C0 vs C4	96.51	96.89	-0.3770	1.271	3	3	0.2966	10

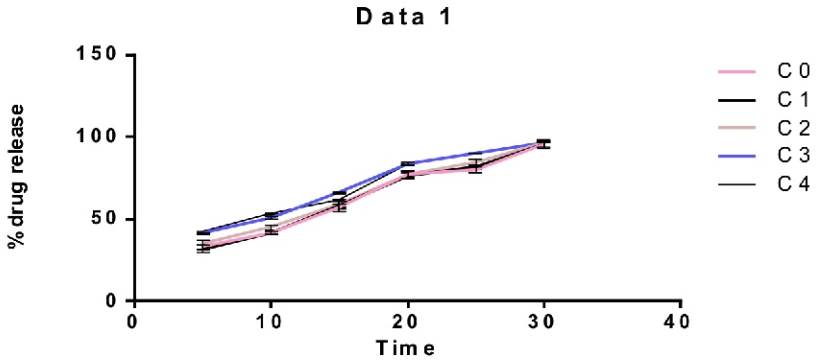

Fig 13. : Comparative % cumulative drug release from complexes and drug in 0.1 N HCl

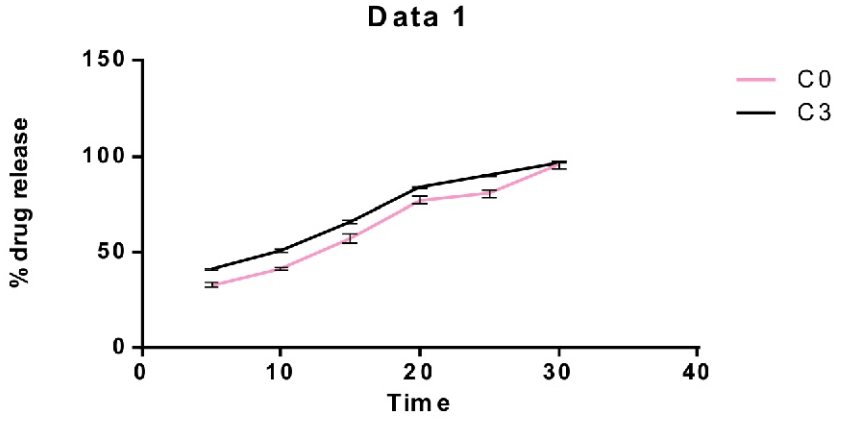

Fig 14. : Comparative % cumulative drug release from selected C3 complex and drug in 0.1 N HCl

Evaluation of formulation

Table 20. : Evaluation of formulation

Sr.No.	Evaluation Parameter	Formulations			
		F1	F2	F3	F4
1	Appearance	Slightly Yellowish Oval shape Smooth	Slightly Yellowish Oval shape Smooth	Slightly Yellowish Oval shape Smooth	Slightly Yellowish Oval shape Smooth
2	Hardness (kg/cm^2)	2.75±0.6	2.72±0.4	2.73±0.2	2.70±0.3
3	Thickness (mm)	4.81±0.4	4.89±0.5	4.80±0.4	4.88±0.5
4	Friability (%)	0.59	0.62	0.59	0.50
5	Dispersion time (s)	38±2.30	35±2.92	32±1.45	30±3.62
6	% weight variation	204±1.56	202± 0.56	202±0.46	200±0.030
7	Wetting time (s)	36±1.86	38±2.08	34±0.654	32±1.660
8	Wetting volume	4.4±0.754	4.5±1.65	4.4±0.546	4.2±0.22
9	Uniformity of dispersion	Passes	Passes	Passes	Passes

Table 21. : Average bitterness values of formulation with plain drug

Formulation	Pure drug tablet	F1	F2	F3	F4
Average bitterness value	5	1.11	1.11	1.19	**1.11**

Taste evaluation of formulation

All four formulation of Drug:βCD complex of montelukast sodium:βCD (1:1) was subjected to the taste evaluation by a panel of nine members with respect to bitter taste. The average bitterness value of all four formulations is shown in (Table 21).

As shown in above table, taste of montelukast sodium is masked in the F4 formulation by Beta-cyclodextrin.

Release rate study of formulation:

In vitro dissolution of optimized dispersible tablet i.e. formulation F4 drug: βCD was carried out using USP dissolution rate test apparatus II (Model: Dissolution 2000, Lab India) in 0.1 N HCl and simulated gastric fluid, 10 ml of the aliquot were withdrawn at different time interval of 5, 10, 15, 20, 25 and 30 min and the replacement was made each time with 10 ml of fresh

Table 22. : Percent cumulative drug release from formulation (F4)

Time (min)	Percent drug release (0.1 N HCl)
5	36.20±0.46
10	46.35±0.34
15	61.90±0.87
20	79.13±1.56
25	87.40±1.45
30	98.90±0.49

From above drug dissolution data of optimized batch, F4 shows 98.90% drug release within 30 min in 0.1 N HCl.

dissolution medium. Each of 10 ml of sample was filtered through Whatman filter paper. The absorbance was measured at respective wavelengths. The drug concentration in the sample was determined from the standard curve of the drug in 0.1 N HCl.

CONCLUSION

Montelukast sodium drug was selected because of its metallic taste which is a critical parameter in the pediatric population. Preformulation study for drug-polymer compatibility by IR give confirmation about the complex formation as there is a shifting of peaks as compared to pure drug. Drug get complexed with the polymer (βCD) by kneading method by taking various ratios 1:0.5, 1:0.75, 1:1,1:1.25 which were named as C1, C2, C3, C4 respectively & C0 as plain drug formulation. It was confirmed by DSC and UV. Selected polymer βCD applicable for taste masking of montelukast sodium, it was confirmed by taste evaluation of Drug:βCD complex by human panel method. From taste masking evaluation of complex by human panel method, it was observed that as the concentration of polymer increases the taste masking was better. From release study following conclusions were made: Amount of polymer affect the release of the drug from complex, as the amount of βCD increases the release of the drug from complex decreases in simulated salivary fluid and phosphate buffer. From the drug dissolution data, the drug release from complex C3 showed more drug release in 0.1 N HCl than C1, C2 , C4, & C0. Four dispersible tablet formulations were made by using the different concentration of super-disintegrant which were named as F1, F2, F3, and F4. F4 having maximum quantity of super-disintegrants showed less dispersion time and sufficient taste masking and therefore it was selected as best formulation. The 1:1 ratio containing formulation showed sufficient taste masking in simulated salivary fluid and sufficient drug release in 0.1 N HCl. Overall it was concluded that the polymer Beta-cyclodextrin causes sufficient taste masking of montelukast sodium.

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