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FORMULATION AND EVALUATION OF TASTE MASKED CACHETS OF KETOPROFEN

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ABSTRACT

Ketoprofen is bitter in taste and is omitted by mostly children. Therfore an attempt has been made to prepare ester prodrug using ethyl alcohol and its bitter taste is masked by using β cyclodextrin. The prepared prodrug is characterized by melting point UV and IR spectroscopy. We also prepared cachets of ketoprofen using β- cyclodextrin as taste masking agent. Sodium carboxy methyl cellulose used as suspending agent, citric acid monohydrate used as pH modifiers. The prepared cachets bitter taste intensity was evaluated using volunteers by comparison of test samples with standard solution containing quinine at various concentration.

KEYWORDS: Ketoprofen, Ester prodrug, Taste masking.

INTRODUCTION

Ketoprofen is very potent and widely used among other clinically used NSAIDs, Literature is abundant with its gastric and other side effects because of free carboxylic group. These reactions range both in severity and frequency leading to GI bleeding, ulceration, and hemorrhage induced by NSAIDs is the inhibition of prostaglandin synthesis as the endogenous prostaglandins are known to have cytoprotective action on the gastric mucosa. It has also been accepted that GI lesions produced by NSAIDs[1] are the result of two different mechanisms, a direct contact effect and a generalized systemic effect which may be manifested after absorption following intravenous dosing. This type of damage could be prevented if the carboxylic acid group functionally be masked and therefore the use of

prodrug has postulated as an approach to decrease the GI toxicity due to the direct contact effect.[2] The Purpose of this investigation was to synthesis various ester prodrug using ethyl alcohol and butyl alcohol and characterize by Physicochemical, spectral (UV, IR) and elemental analysis inorderto estabilise their assigned structure. Furthermore the Profens are omitted by children so an attempt has been made that the prepared cachets of ibuprofen taste intensity was evaluated using volunteers by comparison of test samples with standard solution containing quinine at various concentrations.[3]

MATERIALS AND METHODS

Ketoprofen was gift sample from Torrent, Gujarat,Kadi,dist Mehsana,India,β-Cyclodextrin from sigma Aldrich Bangalore, india, Quinine sulphate purchased from S.D. Fine chemicals, Mumbai, India. All other chemicals used were of analytical grade. All melting point were determined by open capillary tubes and are uncorrected.

Synthesis of Ketoprofen alkyl esters

Ketoprofen ethyl ester ester was synthesized by a general method for esterification. Ketoprofen (1.5g) was solubilized in 25 ml of alcohol in a round – bottom flask. Sulphuric acid was added as a catalyst for esterification. The mixture was refluxed for 4h at about 70º C for ketoprofen ethyl ester, and at 80˚ C for Ketoprofen butyl ester with stirring. sodium acetate (0.5g) was added to quench the catalyst and the residual alcohol was removed by vacuum evaporation. The crude product was purified by silica gel column chromatography by eluting with petroleum ether/ethyl acetate (9:1v/v). The identies of the products were determined by IR. To quench the catalyst and the residual alcohol was removed by vacuum evaporation. The crude product were purified by silica gel coloumn chromatography by eluting with petroleum ether/etheylactate(9:1v/v) The identities of the products were determined by UV and IR spectra. Ketoprofen ethyl ester and butyl ester were obtained in the yield of 92 and 91% respectively the nature, melting point and percent yield, he UV λ ax, UV olar absorptivity and IR Characteristics(c=0 strectching vibration) are reported in Table 1.

Characterisation of Prodrug: Melting Point (mp): Veego VMP-PM digital melting point apparatus, uncorrected. For UV spectrophotometric characterisation, solution of ester prodrugs of Ketoprofen 25 µg/ l were prepared in ethanol and water 3:1 and s anned in the range of 200 – 400nm. FT-IR spectra of Ketoprofen ester Prodrug were obtained using the KBr disc technique.

Hydrolysis Studies: Hydrolysis studies were carried Out in aqueous buffer so as to study whether the Prodrug hydrolyse in aqueous medium and what extent, or not, suggesting the fate of the Prodrug in the system. Hydrolysis kinetics of the synthesized Ketoprofen, prodrugswere studied in aqueous buffer solution at pH 7.4. Under experimental conditions the target compounds hydrolysed to release the parent drug as evident by UV analysis. At constant pH and temperature the reaction displayed strict first order kinetics as the Kobs was found to be fairly constant. The data are given in Table 2.

To examine the degradation ester prodrugs in pH as that in stomach, pH 1.2 was selected. An assay time of 2h was selected, after which time stomach emptying would normally be effectively complete. The Ketoprofen ester prodrugs did not hydrolyse to release the parent compound suggesting that they are stable at the gastric pH. At pH 7.4 the ketoprofen ester prodrug hydrolysed to parent compound indicating that the Prodrug will undergo hydrolysis in the system easily.

Table 1: Nature, Melting Point and % Yield, UV and IR Characterization of Ester Prodrugs of Ketoprofen.

Prodrug	Nature	M. point	%yield	λmax	E (L/Cm.mole)	C=O Str.Vibration Cm-1
EtEs KPP	Solid	46-48	92.00	263.7	254	1734.09
BtEs KPP	Solid	47-48	91.00	263.5	302	1736.09

Table 2: Hydrolysis of Ibuprofen, Ketoprofen Ester Prodrug a Mean of Three Sets of Experiments.

Compound	Kobsa ± SD Phosphate buffer (pH 7.4)	Hydrochloric acid buffer (pH 1.2)	t1/2(min) phosphate buffer (pH 7.4)
Et Es KPP	0.005 ± 0.006	----	84.5
Bt Es KPP	0.007 ± 0.004	----	82.5

Anti- inflammatory activity

The inhibition of swelling in carrageenan – induced edema10 in rat paw about by oral administration of the drugsis shown in table-3. The per entage of Swelling inhibition was calculated using the equation inhibition % = {[(Vt –V0) control–(Vt–V0)treated] /(Vt–V0) control}x100 Where in V0 and Vt release to the average volume in the hind paw of the rats (n=6) before any treatment and after anti inflammatory agent treatment respectively.

All the Two ester prodrugs showed better activity compared to the free parent drug. The

maximum anti-inflammatory activity was observed at 3h and remained practically constant up to 6 - 8 h. The anti-inflammatory activity of free ketoprofen, decreased with time. Statistical significance testing using one way analysis of variance showed that the anti-Inflammatory activities of the parent drug and its ester prodrugs were effective in comparison with the control group.[4]

Analgesic Activity: The percent protection in mice 11 brought about by administration of the drug is shown in Table 3. All the Ethyl ester prodrugs showed analgesic activity compared to

Ketoprofen. The percent protection was calculated using equation Protection % = 100 – [number of writhing in test/ number of writhing in control x 100].

Ulcerogenic study: The ulcerogenic 12 effect of ketoprofen and Ester prodrugs was studied at a dose of 100mg/kg It was observed that the ulcerogenic dose for the ester prodrug was approximately four times the dose of ketoprofen. All the animals treated with Ethyl, Ester ketoprofen and compared with animals treated with ketoprofen. All the animals treated with Ethyl Ester ketoprofen did not develop ulcers as they did not hydrolyse in gastric pH. These findings suggest successful masking of the carboxylic function of ketoprofen.

Table 3: Pharmacological Profile of Ibuprofen, Ester Prodrugs

Compound	Oral dose mg/kg^{-1}	Anti inflammatory activity (%inhibition of oedema)[a]		Analgesic activity (% analgesia)[a]	b Ulcer index
		3h	24h		
ketoprofen	20	50.5	33.56	23.42	13.54 ± 0.45
Et Es KPP	20	47.05	32.04	28.54	Nil
Bt Es KPP	20	53.43	32.36	35.75	Nil

a Statistical analysis was performed with ANOVA Followed by t-test, $P < 0.001$. b Dose: 100 mg kg-1 for ulcerogenic activity.

Preparation of physical mixture: The following system of Et, Es KPP, , Bt Es KPP and CD were prepared in 1:25 molar ratio.

Physical mixture (PM): The physical mixture of Et, Bt Es KPP, and CD was obtained by mixing individual components geometrically that had previously been sieved through sieve no 44, together with a spatula. Fourier Transform Infra-red Spectroscopy (FTIR) FTIR transmission spectra were obtained by using KBr discs by means of hydrostatic press. The

scanning range was 400 to 4000cm-1 .The characteristics peaks were recorded. Differential Scanning calorimeter (DSC) was performed using Differential Scanning Calorimeter (Mettler Toledo, DSC 822). Samples were heated in an open alu iniu pans at a rate of 5 per in-1 under a nitrogen flow of 40 ml/min.

Preparation and Evaluation of the Dry Suspension: Dry suspension powder containing equivalent of 100 mg of Et, Bt Es KPP were prepared from Et, BtEs KPP, and Physical mixture. Sodium carboxy methyl cellulose (HVP) was used as suspending agents. Citric acid monohydrate was used as Ph modifier. The following procedure was applied to prepare a suspension powder. The smallest amount of physical mixture was mixed with the same amount of another excepient, following the principle of geometric dilution. To prepare the reconstituted suspension, an appropriate 10 ml of water was added to the suspension powder and stirred with glass rod until a homogenous product was obtained (Table 4 & 5).

Angle of Repose: For measurement of angle of repose of suspension powder, they were passed through a funnel on the horizontal surface. The height (h) of the heap formed was measured with cathetometer and the radius (r) of the cone base was also determined. The angle of repose Φ was al ulated fro following equation: Φ tan-1(h/r).

Sedimentation Characters: To study the sedimentation in suspension, the sedimentation volume was determined as function of time. The sedimentation Volume, F is defined as the ratio of the final, equilibrium volume of the sediment, Vu to the total volume Vo before settling, as expressed in the following equation: F= (Vu/Vo) In this study, the sedimentation volume was determined as function of time. 10 ml suspension (height = 12cm) was decanted in a cylinder of 10 ml with diameter of 1.5 cm. After 1h, the sedimentation volume F was determined.

Gustatory Sensation Test: Gustatory sensation test was carried out according to the method described by Mou-young et al., 13. Twenty healthy male human volunteers in the age group of 23-27 years were selected based on quinine sensitivity test. The non-taster and super taster were rejected. 1 g of Et,Es KPP each respectively dispersed in 100 ml water for 15 sec. For comparison of pure Bt Es KPP was subjected to taste evaluation by the panel. Immediately after the preparation, each volunteer held about 1 ml of the dispersion in the mouth for 30s. After expectoration, bitterness level was recorded. A numerical scale was used with following values: 0 = tasteless, 0.5 = very slightly bitter, 1 = slightly bitter, 1.5 = slight to

moderate bitter, 2 = moderately bitter, 2.5 = moderate to strong bitter, 3 = strongly bitter, 3+ = very strong. This numerical scale was validated by testing samples randomly. The oral cavity was rinsed with distilled water three times to avoid bias. Wash out period between testing different samples was 15 min (Table 6).

Table 4: Formulation of suspension powder

Drug/Excipients	Per cachet		
	Et Es KPP	BtEsKPP	KPP
KPP (Gms)	-----		
Physical mixture(g)	0.175	0.175	------
Xanthan gum (g)	0.002	0.002	0.002
Microcrystalline cellulose (g)	0.064	0.064	0.064
Citric acid(g)	0.006	0.0060	0.006
Methyl Paraben (g)	0.002	0.002	0.002
Sunset Yellow FCF (g)	0.001	0.001	0.001
Total Filled weight per cachet(g)	0.250	0.250	0.250

Table 5: Physical Properties of Suspension Powder

Parameters	EtEs KPP	BtEs KPP	KPP
Angle of repose Θ ± Da			
F Value after reconstitution ± SDa	36.32±0.53	37.78±0.46	37.68±0.52
pH after (reconstitution)	4.6 - 4.7	4.6- 4.7	4.6 – 4.7

Table 6: Bitterness Score Evaluation by a Panel of Twenty Human Volunteers

	Number of Volunteers rating the preparation as							
Formulation	0	0.5	1	1.5	2.0	2.5	3.0	3.5
KPP								
ET ES KPP	20					1	17	2
BT ES KPP	20					1	17	2

Gustatory Sensation test for Suspension Powder: The prepared suspension powders were subjected to taste evaluation by the same panel of twenty selected volunteers. for formula 1,2 10% of panel rated it as very strongly bitter, 85% strongly bitter and 5% moderate to strong bitter while all the other formula 3,4,5,6 was rated as tasteless by 100% of volunteers of panel (Table 6).

CONCLUSION

The Study conclusively demonstrated the complete masking of bitter taste of prepared Et, BtEs KPP, with cyclodextrin in suspension. The FTIR and DSC studies indicated inclusion complexation in Physical mixture. The taste masking is due to CD enwraps bitter tasting

drugs, impeding its interaction with the taste buds. Further the sweet taste of CD imparted additive effect.

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