INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

AN ENDEAVOUR TO MASK THE BITTER TASTE OF TRAMADOL HCL BY ION EXCHANGE TECHNIQUE

G.S. Dash[1*], P.N. Murthy[2], K.A. Chowdary[3] and Biswaranjan mohanty[4]

[1]Hi-Tech College Pharmacy, Bhubaneswar, Odisha, India.
[2]Royal college of Pharmacy and Health Sciences, Berhampur, Odisha, India.
[3]St. Ann's College of Pharmacy, Vizianagaram, A.P., India.
[4]Institute of Pharmacy and Technology, Salipur, Cuttack Odisha, India.

ARTICLE INFO

Article history
Received 25/11/2021
Available online
05/01/2022

Keywords
Taste Masking,
Tramadol Hydrochloride,
Ion Exchange Resins,
Resinate,
Palatability.

ABSTRACT

The rationale of this research work was to mask the bitter and unagreeable taste of Tramadol HCl which will improve the organoleptic and physicochemical properties such as taste, feel and other molecular properties of drug by making complexes with ion exchange resin (IER) on the basis of ion exchange technique. Tramadol HCl is a central acting opoid analgesic. In this work an effort has been shown to formulate a bitter less form of the drug which can be acceptable for oral administration with enhanced palatability and patient compliance. Indion-234, Tulsion-335 and Tulsion-344 were the three ion exchange resins chosen for preparation of drug resin complex (DRC) or resinate and on the basis of drug loading Tulsion-335 selected as the best among them. The ratio of drug and resin (Tulsion-344) in 1:2 had shown excellent drug loading and taste masking ability. The confirmation of complexation between drug and resin was confirmed by infrared spectroscopy, thermal analysis and x-ray diffraction. Infrared spectroscopy revealed the complexation of Tramadol HCl with Tulsion-344 IER. The thermal analysis (differential scanning calorimetry-DSC) has shown a sharp change in endothermic peak between drug and drug resin complex (DRC).The x-ray diffraction pattern of DRC signified complete disappearance of crystalline peaks of drug. The crystalline form of the drug changed to amorphous form was confirmed by these two tests. The extent of taste masking ability of drug resin complex (resinate) was assured by time intensity method followed by determining the amount of drug release in phosphate buffer of pH 6.8(simulated salivary fluid) and 0.1N Hydrochloric acid (simulated gastric fluid) and the results authenticated the successful masking of bitter taste of the drug. This taste masked drug resin complex (resinate) will be a tool to fabricate fast disintegrating tablets which will mitigate swallowing problem in pediatrics and geriatrics patients and will provide better palatability to liquid dosage forms.

Corresponding author
G. S. Dash
Department of pharmaceutics,
Hi-Tech College Pharmacy, Bhubaneswar,
Odisha, India.
91 9937178954
dashgyana09@gmail.com

*Please cite this article in press as **G. S. Dash** et al. An Endeavour to Mask the Bitter Taste of Tramadol Hcl by Ion Exchange Technique. Indo American Journal of Pharmaceutical Research.2021:11(12).*

INTRODUCTION

Masking the unpleasant taste characteristic of the drug is an important factor for oral administration. The ingested material's Palatability is extremely important factor in determining the acceptance rate of the ingest pharmaceuticals especially for pediatric and geriatric population (1). Tramadol HCl is a white, bitter, crystalline and odourless powder having a better analgesic activity. Its oral bioavailability is around 76% and has a volume of distribution of approximately 2.7 lit/kg (2).Fast disintegrating tablets and liquid dosage forms of this drug is a challenge due to its extreme bitter taste. Many methods are there to achieve an acceptable palatability. The addition of flavours or sweetening agent or by increasing the viscosity of formulation may not be sufficient enough to mask the taste of drug and requires the use of some other technological processes (3).More than 60 percent of the pharmaceutical products are taken orally. So the unacceptable taste is one of the important formulation problem encountered with such oral products(4).Fast disintegrating tablets are having more porosity in the tablets which will decrease the disintegration time(5).Superdisintgrants are used that swell or absorb water rapidly to disintegrate the tablets(6).Such tablets dissolve fast and exert rapid onset of action(7).Numbers of techniques are there for bitterness inhibition such as the use of cyclodextrin for making inclusion complexes(8),viscosity modification to affect rheological properties(9),melt granulation(9) and ion exchange resin(10).Therefore, the taste masked formulation is a challenge to the formulator(11,12).Now the fast disintegrating tablets(FDT) is the most preferred commercial formulation(13,14).Better ion exchange efficiency ,stability and insolubility of ion exchange resins have made them suitable candidates for taste masking. Initial screening of various ion exchange resin like Indion-234,Tulsion-335 & Tulsion-344 grade showed different efficiency of drug loading by making complexes with drug.Tulsion-344 was selected as the IER of choice by considering the efficiency of drug loading and taste masking ability. It is a weak cationic IER with sulfonic functionality and has a better ability to form bitter less resinate by complexation with intensely bitter drugs.

MATERIALS AND METHODS

Materials

Tramadol HCl (Zydus Cadila Health Care,Ahmedabad,India), Indion-234(Ion Exchange India ltd., Mumbai), Tulsion-335 & Tulsion-344(Thermax India Ltd., Pune) were procured as gift sample. All other chemicals used in the work were of analytical grade and purchased locally.

Methods

Determination of threshold concentration of Tramadol HCl for bitterness (15)

Threshold bitterness concentration is the minimum concentration at which bitterness starts to be perceived and continues to sustain after 20sec at least. Nine healthy human volunteers (age 20-30yr) were selected for taste evaluation. A series of solution of different concentration 10,20,30,40 &50 µg/ml of Tramadol HCl was prepared by using distilled water. The nine taste panel volunteers were asked to hold 10 ml of each solution in mouth for 30sec and rate the taste on a scale from 0 to 4(0-no bitterness, 1-slight bitterness, 2-bitter, 3-moderate to strong bitterness and 4-very strong bitterness).The volunteers rinsed their mouth with distilled water and waited for 30 mints before tasting the successive samples. After each test the perception of degree of bitterness of the drug solution was estimated by the rating of taste panel volunteers and the threshold concentration of bitterness determined.

Preparation of resinate (16, 17)

Resinate (drug resin complex-DRC) was prepared using batch process.10gm of Tulsion-344 was taken and kept in a beaker containing 250ml. of deionised water for 60 min to swell up to the highest limit. Then 5gm of Tramadol HCl was added to 4% resin slurry and stirred by a magnetic stirrer for 6 hr. Through a whatman filter paper, the mixture was passed and filtered. The residue was washed with 100 ml. of deionised water and dried at 50 ℃ to constant weight.

Effect of various Parameters on drug loading and their optimization (18, 19)

For maximum drug loading the parameters like activation of resin, pH and its swelling time were optimized.

For activation of resin 4gm of Tulsion-344 was placed on a whatman filter paper in a funnel which was washed with distilled water and subsequently with 100ml of 1N HCl. The resin was washed again and again with distilled water until neutral pH was reached. The resinate(DRC) with activated resin was prepared in identical manner as described earlier under the heading of preparation of resinate. In the same way the resin was treated with 1N NaOH for alkali activation. Finally the resin was activated with combined treatment of 1N HCl and 1N NaOH solution. Drug loading was checked and compared for each individual treatment.

To determine the effect of pH on drug loading, the drug solutions having pH 2, 3, 5, 7 and 9 were prepared with distilled water and pH was adjusted by using standard solution of HCl and NaOH. Same quantity of activated resin swollen separately for 60 min each and added to drug solutions of different pH .The drug loading efficiency was estimated in different pH condition.

To study the swelling time 4gm of activated Tulsion-344 was taken individually in five beakers. Then to each beaker 100ml of distilled water was added and kept for 15, 30, 60, 90 &120 min. DRC was prepared as described earlier and the efficiency of drug loading with swelling time was determined

Confirmation of complex formation (19)

Fourier transform infrared spectroscopy (FTIR)

Fourier transform infrared spectroscopy (FTIR) studies of drug (Tramadol HCl), resin (Tulsion-344), drug resin physical mixture and resinate (DRC) have been carried out with optimized drug resin ratio by using Shimadzu, IR Affinity-1 model. Samples were prepared using KBr in powder form in sample holder(1:20) and spectra were recorded in the range of 500 to 4000cm^{-1}.Spectra were compared and analyzed on the basis of the functional group of drug and resin involved in complexation.

Thermal analysis(DSC)

Differential scanning calorimetry (DSC) was carried out to analyze the thermal characteristic of drug and resin and their complexation by using Shimadzu,DSC-60 model .The samples were hermetiacally sealed in aluminium pans and heated over the temperature range 10ºc to 300ºc with heating rate of 10ºc/min. The glass transition behavior was analysed by purging Nitrogen gas (20ml/min).

Powder X-ray diffraction(P-XRD)

X-ray diffraction studies (XRD) of Tramadol HCl, Tulsion-344 and resinate (DRC) have been carried out by using X-ray diffractometer with Phiips power generator and analyzed for interactions between drug and resin to confirm the changes in crystallographic nature by complexation.

Drug content

This estimation was carried out to determine the actual drug content per weight of the dry resinate. DRC(resinate) of 100mg was added to 100ml of 0.1N HCl and stirred for 60 min to release the total drug from resinate. The mixture was filtered and 1 ml of the filtrate was diluted suitably by using 0.1N HCl. The absorbance of this solution checked at 272nm spectrophotometrically (UV-1800, Shimadzu, Japan) treating 0.1N HCl as blank and the content of drug was evaluated.

In vivo taste masking studies (20)

Taste masking ability of DRC was estimated by panel of nine healthy human volunteers of age 20-30 years using time intensity method. The written consent was obtained from the volunteers after explaining the detail study protocol. DRC equivalent to 50mg of Tramadol HCl was held in the mouth for 10s by each individual .Bitterness level were recorded with the help of a numerical scale from 0 to 4(0-no bitterness, 1-slight bitterness, 2-bitter, 3-moderate to strong bitterness and 4-very strong bitterness).

In vitro taste masking studies (15)

Drug release from DRC (resinate) in Phosphate buffer of pH 6.8 was treated as in vitro taste masking studies for taste evaluation. A quantity of resinate equivalent to 50mg of Tramadol HCl was added to a volumetric flask containing 10 ml of phosphate buffer of pH 6.8.The mixture was shaken for 180sec and filtered. Content of drug in the filtrate was estimated spectrophotometrically. The amount of drug dissolved should be less than the threshold bitterness concentration of the drug after 120sec.

In vitro release studies (19)

In vitro release studies is the dissolution studies of the drug .DRC equivalent to 50 mg of Tramadol HCl was weighed accurately and added to 900ml of 0.1N HCl treated as dissolution medium in a USP type-II dissolution apparatus(Electrolab,model TDT-08L) at 37±0.5ºC at 70 rpm for one hour. Aliquots were withdrawn at specific time intervals and replenished with the same volume of fresh 0.1N HCl. Aliquots after suitable dilution were analyzed spectrophotometrically at 272nm and the amount of drug released from DRC was estimated.

Stability studies

The stability studies were carried out according to the ICH (international conference on harmonisation) guidelines for climatic zone-III. DRC of optimized batch was exposed to stability test inside a stability chamber (Labline, India) at 40ºc±2ºc / 75%±5% RH for a period of three months. After every month samples were analyzed for physical changes and in vitro drug release.

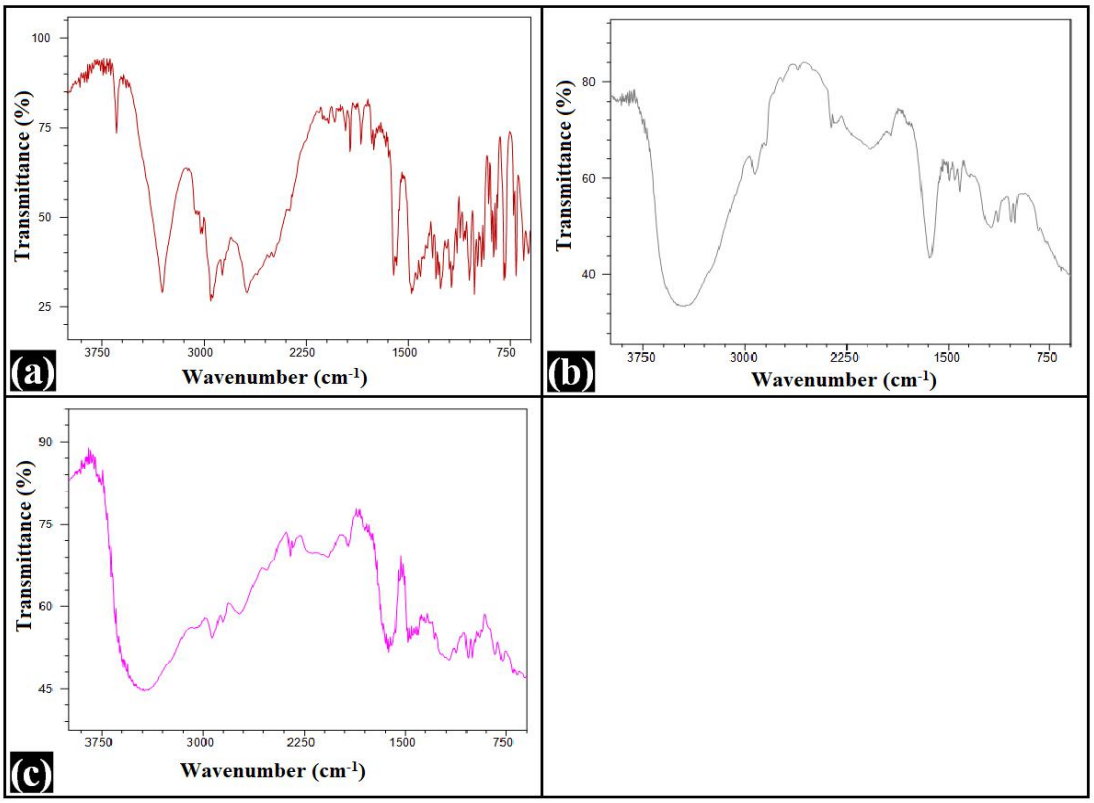

Figure 1 FTIR Spectra of Tramadol HCl (a), Tulsion 344 (b) and DRC (c)

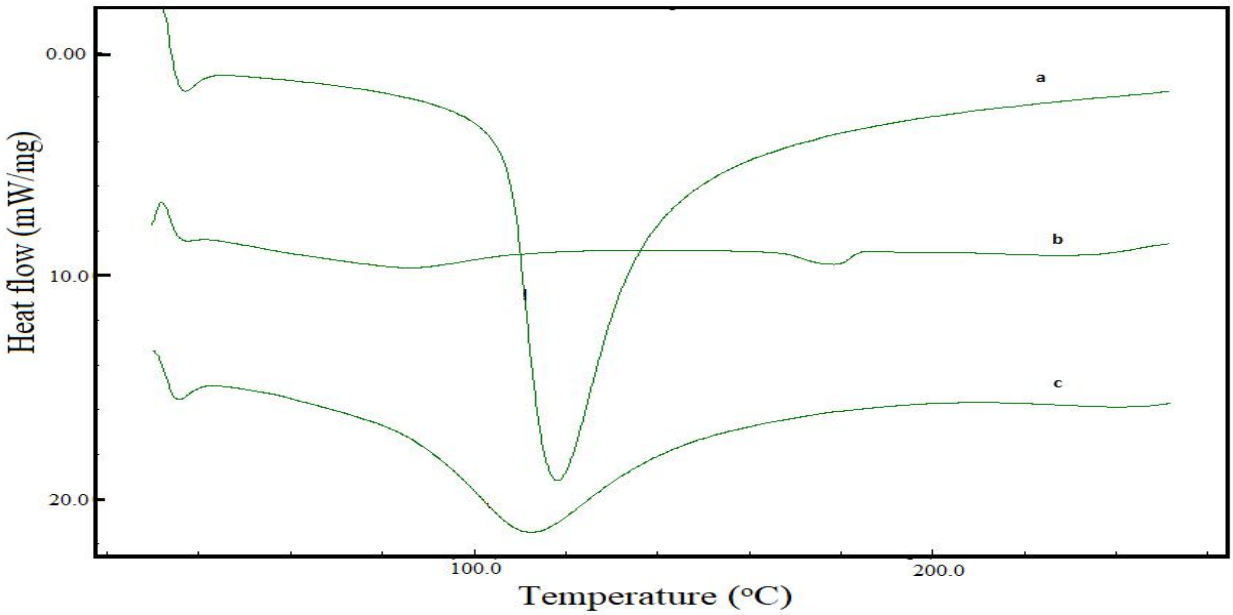

Figure 2 DSC thermograms Tramadol HCl (a), Tulsion 344 (b) and DRC (c).

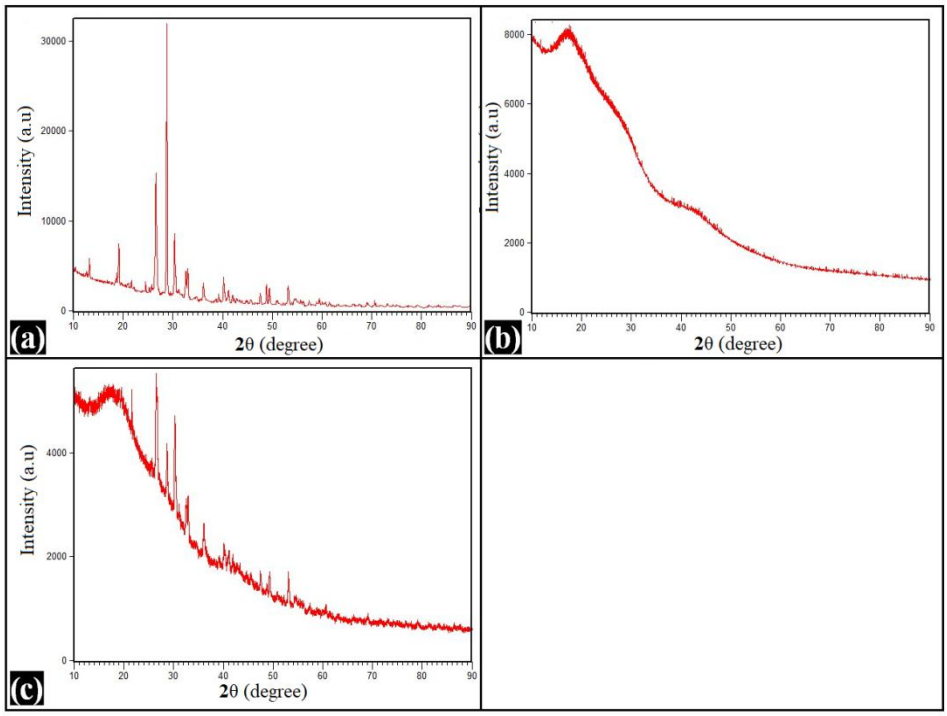

Figure 3 XRD patterns of Tramadol HCl (a), Tulsion 344 (b) and DRC (c).

RESULT AND DISCUSSION

Threshold bitterness concentration

The minimum concentration of Tramadol hydrochloride which produces perception of bitter taste was found to be 20µg/ml and referred as threshold value as mentioned by the human volunteers.

Effect of various Parameters on drug loading and their optimization

The drug loading efficiencies with inactivated resin, acid activated resin, alkali activated resin and by both acid alkali activated resin was ascertained to be 84±1.4%, 89±1.2%, 91±2% and 94.5±0.4% respectively. The maximum drug loading on resin was obtained when treated with combination of both acid and alkali for activation. On activation of resin more exchangeable groups are available for maximum drug loading. When the drug loading was checked on different pH of 2, 3, 5, 7 and 9 the percentage of drug loaded found to be 82.4±0.5%, 85.6 ±1%, 92.4±2%, 94.2±0.3% and 94.2±0.4% respectively. The result confirmed that the drug loading efficiency was maximum at neutral range of pH and remained merely equal on further increase in pH. The drug loading percentage with respect to swelling time 15, 30, 60, 90 and 120 min were found to be 81.8±0.7%, 90.6±0.8%, 94.3±0.5%, 94.35±1 % and 94.39±0.8% respectively. It was observed that 60 min of swelling time showed merely same extend of drug loading as that of 90 and 120 min. So 60 min of swelling time is sufficient and optimum for maximum percentage of drug loading. The surface area and exchangeable groups of resin get exposed to outside by swelling. As a consequence the drug loading efficiency has enhanced.

Confirmation of complex formation

FTIR Interpretation:

The Infrared spectra of Tramadol HCl(drug),Tulsion-344 and drug resin complex(DRC) are depicted in Fig. 1. Drug spectrum showed few prominent peaks at 3635.82 cm^{-1}, 3300.20 cm^{-1} and 3039.81 cm^{-1} due to O-H,C-N and C-H stretching respectively. These mentioned peaks of drug were not seen in the spectrum of drug resin complex (DRC) which gave evidence that the drug was firmly entrapped in the polymer matrix of resin and had made complex.

Thermal analysis / (DSC) Report:

The DSC thermogram of Tramadol HCl(drug),Tulsion-344 and drug resin complex(DRC) are illustrated in Fig. 2.An intense and sharp endothermic peak was observed at 178.4ºC where as no endothermic peak was detected for Tulsion-344 (resin) and a very diffused peak noticed for DRC (resinate) at 129ºC. The shifting of thermogram of DRC to a lower temperature confirming it´s amorphous nature and complexation.

X-ray diffraction (XRD) interpretation:

XRD of Tramadol HCl(drug),Tulsion-344 and drug resin complex(DRC) are depicted in Fig. 3 .The drug, resin and complex were compared for their crystalline and amorphous nature. The X-ray diffractograms of drug showed numbers of intense and sharp peaks which confirmed it's crystallinity. On the other hand resin and resinate had shown diffused peaks. The absence of characteristic peaks of the drug in DRC (resinate) represents it's amorphous nature. The crystallinity of drug converted to amorphous form in the complex may be due to the molecular dispersion of drug in the polymeric matrix of resin.

Drug content

The percentage of drug loading was estimated and found to be 95.79% after optimizing all the parameters. So the drug content calculated from percentage of drug loading and was 31.93% (w/w).

In vivo taste masking studies

The numerical taste evaluation value by human volunteers was less than one which justified the taste masking efficiency of DRC. Bitter less DRC was our target to enhance palatability and achieved. The acceptance rate will increase further by incorporating sweetening agent and flavourant in the formulation.

In vitro taste masking studies

After 150sec in Phosphate buffer of pH 6.8 the amount of drug (Tramadol HCl) released was below the threshold bitterness concentration to impart bitter taste. This result confirmed that the DRC has released very less amount of drug in salivary pH (mouth).So the taste of the drug is not detectable in oral cavity when it is swallowed. Hence the drug and resin had made a satisfactory complex.

In vitro release studies

The dissolution studies showed that in 0.1N HCl more than 90% of the drug was released from DRC in 15 minutes and completely released within 30 minutes. These results indicated that the rate of drug release in 0.1N HCl (acidic medium) treated as simulated gastric fluid is very fast.

Stability study

The DRC (resinate) of optimized batch has not shown any physical changes and the drug release profile from DRC is merely identical after three months of stability testing. So it confirmed the stability of prepared DRC.

CONCLUSION

The ion exchange technique implemented for masking the bitter taste of Tramadol HCl by forming an ion exchange resin complex with Tulsion-344 was excellent and satisfactory. The batch process of complexing the drug with resin provided an efficient percentage of drug loading. The DRC (resinate) was not breaking in saliva (pH-6.8) where as in acidic medium (pH-1.2) more than 90% drug released within 15min. So the human volunteers were not able to perceive any bitter taste and rated the complex as tasteless and agreeable. The prepared DRC will provide better palatability and patient compliance to the formulation of fast disintegrating tablets and liquid dosage forms of Tramadol HCl.

ACKNOWLEDGMENTS

Authors are thankful to Zydus Cadila Health Care, Ahmedabad, India for providing Tramadol HCl as gift sample. Authors also wish to acknowledge Ion Exchange India Ltd., Mumbai and Thermax India Ltd., Pune for providing ion exchange resins Indion-234 and Tulsion-(344 & 335) respectively as gift samples. Authors are grateful to all who have helped directly or indirectly to carry out this research work.

REFERENCES

1. Roy GM. Taste masking in oral pharmaceuticals.Pharm.Tech 14:EUR.24-35.
2. http://pubchem.ncbi.nlm.nih.gov
3. Shimano K, Kondo O, Miwa A, Higashi Y and Goto S. Evaluation of uniform sized microcapsules using a vibration nozze method. Drug Dev. Ind. Pharm 1995; 21:331-347.
4. Lachman, Liberman HA and Anig JL.Theory and practice of industrial pharmacy.3rd ed. Mumbai: Varghese Publishing House 1991; 296-302.
5. Biradar S, Bhagavati S and Kuppasad.Fast dissolving drug delivery system: a brief overview. Internet J P harmaco.2006; 4(2).
6. Chang R, Guo X, Burnside B, Couch R. Fast-dissolving tablets. Pharma Techno 2000:24(6):52-8.
7. Bagul U et al. Manufacturing technologies for mouth dissolving tablets. www.pharmainfo.net.2006;May 31.
8. Motola S, Agisim GR. Palatable Ibuprofen solutions. 1991 US Patent 5,024,997.
9. Blasé CM and Shaw MN. Aqueous pharmaceutical suspensions for pharmaceutical actives.1993 EP application no.0556057 B1 to McNeil-PPC Inc.
10. Lu MYF, Borodkin S, Wooodward L, Li P, Diesner C, Hernandez L et al. A polymer carrier system for taste masking of macrolide antibiotics.Pharma Res 1991; 8:706-712.

11. Bi Y, Sunada H, Yonezawa Y, Dayo K, Otsuka A, Lida K.Preparation and evaluation of a compressed tablet rapidly disintegrating in oral cavity. Chem Pharm Bu (Tokyo).1996; 44:2121-2127.
12. Nanda AR and Kandarapu Garg S. An update on taste masking technologies for oral pharmaceuticals.Indian J Pharm Sci 196;64:7-10.
13. Chang R, Guo X, Burnside B, Couch R.A review of fast dissolving tablets.Pharm Tech.(North America).2000;52-58.
14. Kuchekar B, Badhan A, Mahajan H. Mouth dissolving tablets of Salbutamol suphate: A novel drug delivery system. Indian drugs 2004; 41(10):592-8.
15. Sohi H, Sutana Y, Khar R.Taste masking technologies in oral pharmaceuticals recent development and approaches. Drug Dev Ind Pharm 2004; 30:429-48.
16. Borodkin S, Sundberg D. Poycarboxylic acid ion-exchange adsorbates for taste coverage in chewable tablets.J Pharm Sci 1971; 50:1523.
17. Avari J, Bhalekar M, Cation exchange resins for taste masking and rapid dissolution of sparfloxacin. Indian Drugs 2004; 41(1):19-23.
18. Chaudhari P, Chaudhari S, Lanke S, Patel N. Formulation and in vitro evaluation of taste masked orodispersible dosage form of evocetrizine dihydrochloride. Indian J Pharm Edu Res 2007;41(4):319-28.
19. Piscal S, Zainnuddin R, Nalawade P, Mahadik K, Kadam S. Molecular properties of ciprofloxacin-indion 234 complexes. AAPS Pharm Sci.Tech 2004; 5(4):e62.
20. Fu, Lu Mou-ying et al. A polymer carrier system for taste masking of microlide antibiotics. Pharmaceutical Research 1991; 8(6):706-711.

5487847845**1211107**