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Formulation and Evaluation of Taste Masked Orodispersible Tablets of Ondansetron Hydrochloride

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Abstract:
The demand for mouth dissolving tablets has been growing, during the last decade especially for geriatric and pediatric patients because of swallowing difficulties. The purpose of this research was to mask the intensely bitter taste of ondansetron HCl and to formulate a orodispersible of the taste-masked drug. Taste masking was done by complexing ondansetron HCl with indion204 in different ratios by the solvent evaporation. Drug- resin complex were optimized by considering parameters such as optimization of resin concentration, optimization of swelling time, optimization of stirring time, optimization of pH and optimization of temperature on maximum drug loading. The effects of variables were observed on maximum amount of the drug loading. During preparation of drug resin complex (resinate), the other variables were kept constant. The resinate was evaluated for taste masking, characterized by X-Ray diffraction and infra red spectrometer. In vitro drug release study of taste masked tablet showed that more than 90 % of the drug release within 20 minutes. Thus, results conclusively demonstrated successful masking of taste and rapid disintegration of the formulated tablets in the oral cavity.
Keywords: *Ondansetron HCL, Indion 414, Resinate, Orodispersible*

Introduction:

In recent decades, a variety of pharmaceutical research has been conducted to develop new dosage forms. considering quality of life, most of these efforts have been focused on ease of medication. among the dosage forms developed to facilitate ease of medication, the orodispersible tablet is one of the most widely employed commercial products[1]. the orodispersible has remarkable disintegration properties; it can rapidly disintegrate without water in the mouth within a few seconds. when an orodispersible orodispersible is placed in the oral cavity, saliva quickly penetrates into the pores causing rapid disintegration. orodispersible are useful in patients, such as pediatric, geriatric, bedridden, or developmentally disabled, who may face difficulty in swallowing conventional tablets or capsules and liquid orals or syrup, leading to ineffective therapy, with persistent nausea, sudden episodes of allergic attacks, or coughing for those who have an active life style. orodispersible are also applicable when local action in the mouth is desirable such as local anesthetic for toothaches, oral ulcers, cold sores, or teething, and to deliver sustained release multiparticulate system to those who cannot swallow intact sustained action tablets/capsules.[2]

ondansetron hcl is a potent antiemetic drug indicated for the treatment and/or prophylaxis of postoperative or chemotherapy- or radiotherapy-induced emesis and also used in the early onset of alcoholism. in general, emesis is preceded with nausea and in such condition it is difficult to administer drug with a glass of water; hence it is beneficial to administer such drugs as orodispersible. ondansetron hcl is an intensely bitter drug; hence, if it is incorporated directly into an orodispersible the main objective behind formulation of such a dosage form will definitely get futile. thus in the present study an attempt has been made to mask the taste of ondansetron hcl and to formulate orodispersible with good mouth feel so as to prepare a "patient-friendly dosage form."[3]

Ion exchange resins are water–insoluble, cross–linked polymers containing salt forming groups in repeating positions on the polymer chain. It can be used in the drug formulations to stabilize the sensitive components, sustain release of drug, disintegrate tablets and mask taste.[4] The resin form insoluble adsorbates or resonates through weak ionic bonding with oppositely

charged drugs so that dissociation of drug resin complex does not occur under the salivary pH conditions. Bitter cationic drugs can get adsorbed onto the weak cation exchange resin of carboxylic acid functionality to form the complex which is non bitter. Indion 204 is a weak acid cation exchange resin based on a cross-linked acrylic-copolymer, divinyl benzene matrix containing carboxylic acid functional groups. It combines with high capacity; it is insoluble in all common solvent, having excellent physical and chemical stability and operating characteristics.[5]

Materials and Methods:

Ondansetron Hydrochloride was obtained as a gift sample from Torrent Pharmaceutical Ltd, Gujarat. Resin Indion 204 was gifted by Ion Exchange (India) Ltd. Other chemicals used were of analytical grade.

Preparation of drug resin complex

An accurately weighed amount of resin particles were suspended in deionised Water for 15 min. to allow uniform swelling of polymer, after which Ondansetron Hcl was added and slurry was stirred with the help of Magnetic stirrer for 45 min to allow the maximum adsorption of drug on to the resin. Resinate thus formed was filtered and washed with deionised Water. It was then dried at 50^0C and the drug Content was determined Spectrometrically at 248nm.

Optimization of concentration of resin on drug loading

An accurately weighed amount of Ondansetron Hydrochloride was added to the different concentration of indion 204 for the determination of optimized ratio with maximum drug loading (Fig 1). Amount of maximum bound drug was determined at 248 nm by UV spectroscopy.

Effect of pH on drug loading

A series of solutions were prepared which contained fixed quantity of pretreated resin INDION 204 (2gm) in deionised water and about 1gm of Ondansetron Hcl. The pH of the solutions was maintained at 3, 3.5, 4, 4.5, and 5. The solution along with drug and resin was stirred at a magnetic stirrer for 45min. The resinate was collected by filtration and washed with copious amount of deionised water to remove free and uncomplexed drug, followed by drying at 50^0C. Drug content was determined as mentioned previously.

Characterization of ondansetron HCL-indion 204 complexes.

X-Ray diffraction Study

X-ray diffraction technique method was used for characterization of crystalline substances. This is a rapid, accurate and very sensitive method for the identification of crystalline phase present in the material. Bragg made use of X-ray for study of internal structure of crystal. X-ray is reflected from planes of atoms within the crystal lattice. The condition for reflection is given by well-known Bragg's equation.

$$n\lambda = 2d \sin\theta$$

Where,

λ – wavelength of X-rays.
θ- Angle of incidence
d- Interatomic distance
n- order of diffraction

The samples were analyzed on Philips Analytical- X'Pert.

Taste evaluation:

Evaluation of Taste of Resinate

Taste of resinate was checked by time intensity method. For this purpose 10 human volunteers were selected. In this method a sample equivalent to a normal dose was held in mouth for 10 seconds and volunteers were asked to evaluate the resinate for taste. Bitterness levels were recorded immediately and then at 1, 2, 5, 10 and 15 min. Bitterness values, are based on a 0-3 scale with 3 being – strong bitter, 2 being – moderate bitter, 1 being – slight bitter , X being – threshold bitter, 0 being – tasteless

These volunteers were instructed not to swallow the granules, which were placed on

the tongue. They were instructed to thoroughly gargle their mouth with distilled water after the completion of test.

Determination of drug content:

Resinate so prepared by the batch process, was evaluated for the drug content. 50mg of resinate was stirred with 50ml of Gastric simulated fluid (pH 1.2) till the entire drug was leached out. Then the Suspension was filtered and further dilutions were made. The drug content was noted spectrometrically at 248nm using Gastric simulated fluid (pH 1.2) as blank.

Results are revealed in Table3.

In Vitro drug release study from resinate:

Resinate prepared in 1:2 (drug: resin) ratios at pH 4 was subjected to dissolution in gastric simulated fluid.10mg of drug equivalent resinate was placed in basket surrounded by muslin cloth which retained the formulation The dissolution medium was 900 ml of gastric simulated fluid maintained at $37^0C \pm 1^0C$. The basket was rotated at 50 rpm. The sample (10ml) was withdrawn after every 5 min (For total 20 min) and its absorbance was measured at 248 nm.

The results of the cumulative amount of drug released are revealed in the Figure. 5.

Characterization and evaluation of the tablet blend

Physical properties such as bulk density, tapped density, compressibility index, and the angle of repose of blend were determined.

Formulation and optimization

The tablet consist of resinate equivalent to 8 mg drug.DCP and sorbitol were selected as directly compressible material,indion 414 was selected as super disintigrant. All the six batches were prepared by direct compression method using single punch machine. The hardness of the tablet of each batch were tried to keep constant (3 kg/cm2). The weight of the tablet of each batch was adjusted to 150 mg. The tablet was evaluated for its tensile strength, weight variation, friability, disintegration time**.** **(**Table no 4**).** Dissolution study of tablets was carried out in simulated gastric fluids.

Results and Discussion:

Preparation of resinate

The resinate was prepared by batch process, the weighed amount of resin was stirred for 10-15 minutes for swelling of resin then drug was added to it. The method described for the preparation of drug resin complex mentioned under experimental work was adopted.

Selection of Drug Resin ratio

For the selection of the proper drug resin ratio, the ratio of the drug resin was varied, keeping concentration of drug constant. The pH of the solution was maintained at 4. The result shows that drug resin in the ratio of 1:2 has better drug loading as compared to the other.

The results are shown in Figure 1.

Effect of pH on drug loading

The loading of Ondansetron Hcl onto ion exchange resin is equilibrium process, which depends upon the presence of, cationic form of the drug in the solutions. The presence of cationic form of drug is influenced by pH of the solution, which therefore exerts an influence on loading efficiency. This behavior was investigated by varying the pH of the drug resin solution, keeping the drug resin ratio 1:2 as constant.The result showed that at pH 4 maximum loading of the drug on the resin occurs.(FigureNo.2)

Evaluation of Taste of Resinate

Taste evaluation of DRC was performed by volunteers in the age group of 18 to 22 years. The study protocol was explained and written consent as obtained from volunteers. Resinate equivalent to 8 mg ondansetron hydrochloride was held in the mouth for 5 seconds by each volunteer. Bitterness levels were recorded instantly and then after 30 to 150 sec. The bitterness level was recorded against pure drug using a numerical scale (3 – Strong Bitter, 2 – Moderate Bitter, 1 –

Table 1: Evaluation of taste of resinate

Volunteers	Bitterness level after					
	10 sec.	30 sec.	60 sec.	90 sec.	120 sec.	150 sec.
1	**X**	**0**	**0**	**0**	**0**	**0**
2	**X**	**X**	**0**	**0**	**0**	**0**
3	**0**	**0**	**0**	**0**	**0**	**0**
4	**0**	**0**	**0**	**0**	**0**	**0**
5	**0**	**0**	**0**	**0**	**0**	**0**
6	**0**	**0**	**0**	**0**	**0**	**0**
7	**X**	**0**	**0**	**0**	**0**	**0**
8	**0**	**0**	**0**	**0**	**0**	**0**
9	**0**	**0**	**0**	**0**	**0**	**0**
10	**0**	**0**	**0**	**0**	**0**	**0**

Table 2: Comparison of physical properties of prepared resinate with indion 204

Character	INDION 204	RESINATE
Shape	Irregular	Irregular
Angle of Repose	29.74^{0}	27.54^{0}
Bulk Density	0.75 gm/cm^3	0.78 gm/cm^3

Table 3: Determination of drug content in the optimised resinate

Formulation	Absorbance (nm)	Concentration (ug/ml)	Resinate Required For 8 mg Of drug	Practical yield (%Drug content)	% Drug bound
Resinate (1:2) pH 4	**0.106**	**2.78**	**33.76**	**26.82**	**82.46**

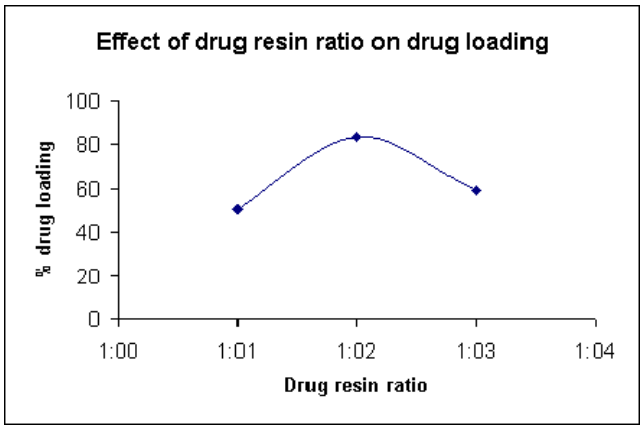

Figure 1: Selection of drug resin ratio

Table 4: Evaluation of optimized batch

Parameter	Optimize batch	Parameter	Optimize batch
Taste	**Sweet**	**Max. Wt. variation (%)**	**4.7**
Mouth feel	**Good**	**Hardness (kg/cm^2)**	**3.2**
Carr's Index	**29.13%**	**Friability**	**0.683**
In vitro disintegration time (sec	**11 sec**	**In vivo disintegration time (sec)**	**26**
Content Uniformity	**99.72**	**$t_{90\%}$ (min)**	**15**

Slight Bitter, X – Threshold Bitter, 0 – No Bitter)(The results are revealed in Table1)

Physical Properties of Resin INDION 204 & Resinate

The results of comparisons of physical properties of resin and resinate are shown in Table 2

Determination of drug content in the optimized resinate

The resinate prepared by selecting 1:2 ratio (drug: resin) at pH 4 was evaluated for drug content. The method described under determination of drug content in resinate mentioned under experimental work was adopted.

X-Ray Diffraction Study

X-ray powder diffraction studies were carried on Ondansetron Hcl and its complex with Indion 204.The drug, resin Indion 204 was subjected to X-ray diffraction study. The drug showed highly crystalline nature and resin Indion 204 showed amorphous nature. The resinate showed non-crystalline characteristics which might be because of entrapment of drug molecule in the polymer matrix of resins. X-ray diffraction pattern of pure Ondansetron Hcl shows sharp intense and characteristic peaks indicating the highly crystalline nature of drug. X-ray diffraction pattern of drug resin complex were found to be diffused, less intense and different, confirming that a new amorphous solid phase had been obtained.(Fig 3)

Dissolution Profile of Resinate

Dissolution of resinate was carried out to observe the release of the drug in resinate. Similar conditions as that of stomach (Gastric Simulated Fluid pH 1.2 without enzyme) was employed in dissolution apparatus. Results indicate that more than 90% of drug was released in 15 minutes, and total drug was released in 20 minutes (Figure4).

Optimization:

While studying the effect of concentration of resin on drug loading, maximum drug loading was found in ratio 1:2 (drug: indion 204). Complexation between the drug and resin is essentially a process of diffusion of ions between the resin and surrounding drug solution. As the reaction is an equilibrium phenomenon, maximum efficiency is best achieved in batch process. Equilibrium time was shorter due to thinner barrier for diffusion of ions, as it is a continuous motion. Also, higher swelling efficiency in the batch process result in more surface area for ion exchange. Hence the batch process is suitable for smaller particles.

The swelling and hydrating properties of Indion 204 affect the rate of ion exchange, which in turn affects the percentage drug loading. In unswollen resin matrix, the exchangeable groups are latent and coiled toward the backbone, hence less drug-loading efficiency. The optimized percentage drug loading (wt/wt) was found to be 83.46±0.16 for Indion 204 with swelling time 30 minute. The equilibrium ion exchange in solution occur stoichiometrically and hence is affected by stirring time**.** Drug complexation involved exchange of ionisable drug and metal ion in resin. Such a mode of complexation between drug and resin affected by pH of media. Complexation was enhanced and was found

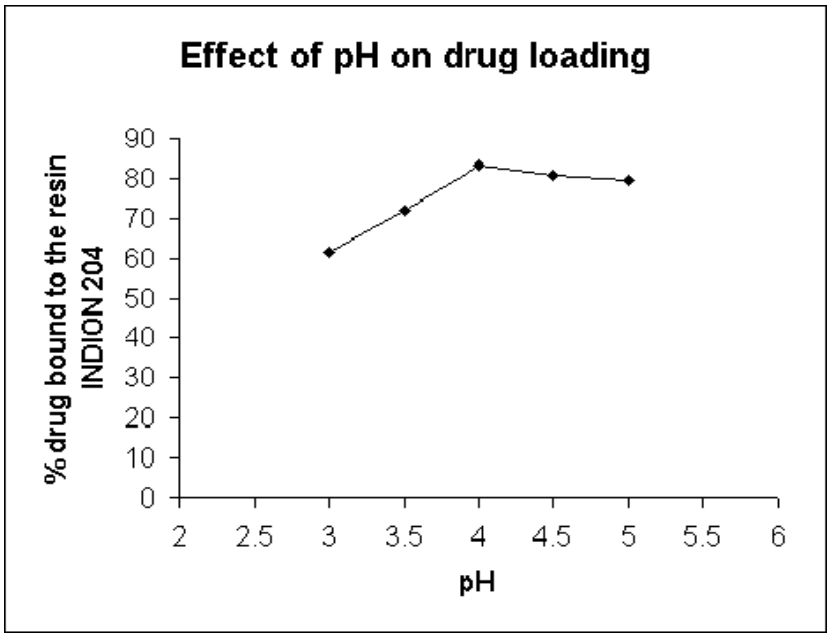

Figure 2: Effect of pH on drug loading

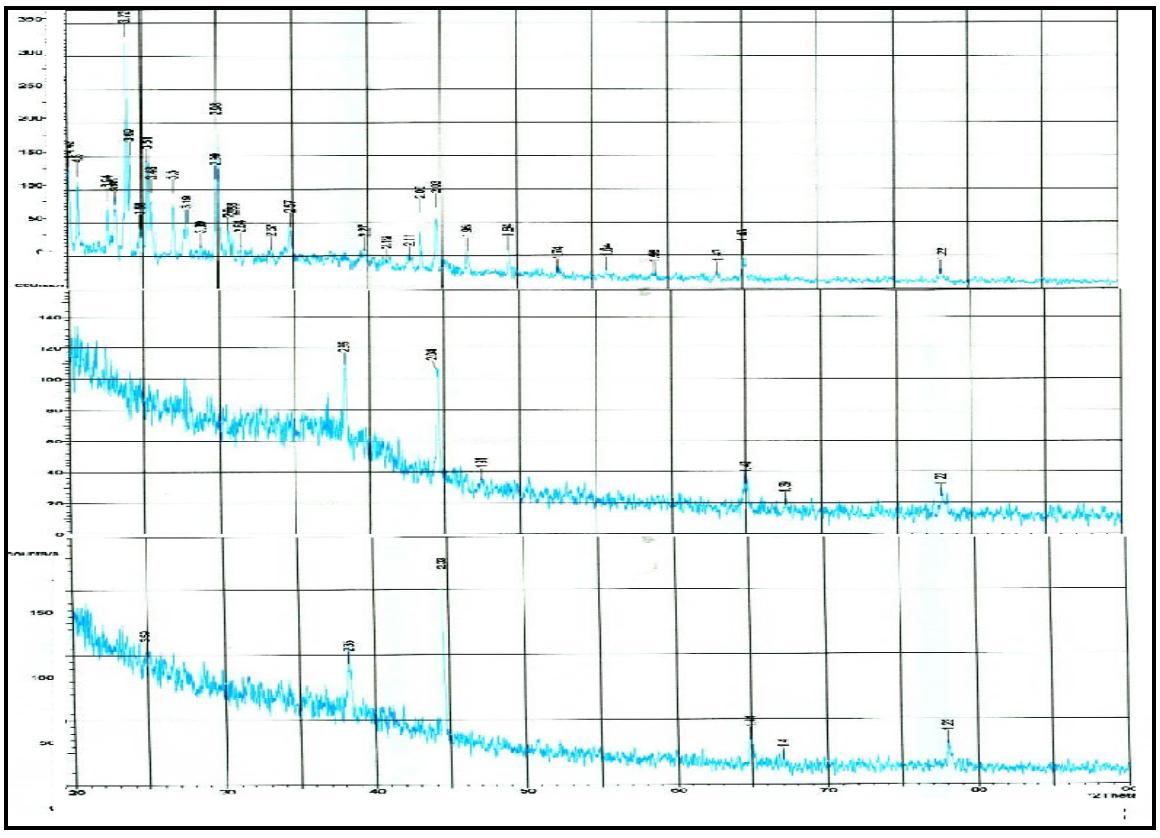

Figure 3: X-Ray diffraction pattern of Ondansetron Hcl Indion 204 & complex

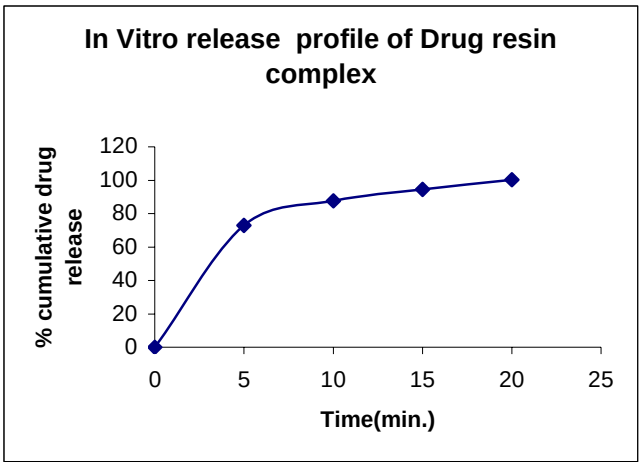

Figure 4: In vitro profile of drug resin complex

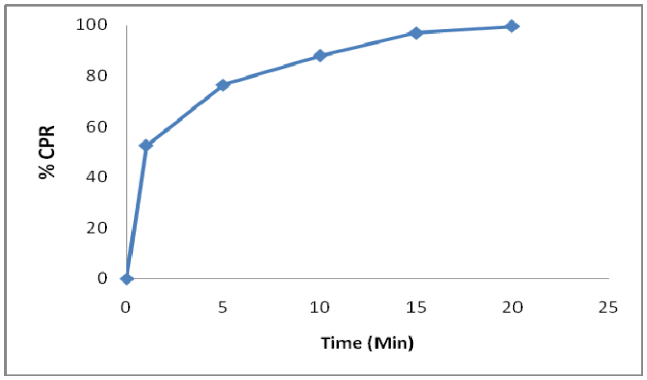

Figure 5: Dissolution study of taste masked tablets

maximum at pH 7. Efficient drug loading on indion 204 in the experimental range 25-80◦C**.** Increased temperature during complexation increases the ionization of drug and resin. The effect is more pronounced for poorly water soluble and unionized drugs. Higher temperature tends to increase the diffusion rate of ions bydecreasing the thickness of exhaustive exchange zone. As ondansetron hydrochloride is water soluble ionizable drug, temperature does not show any significant effect on drug absorption and also cation exchange resins are significantly affected by temperature changes. Dissolution

Dissolution study

The dissolution of Ondansetron Hcl tablets (8 mg Ondansetron = 10mg Ondansetron Hcl) was carried out in paddle type dissolution apparatus. The dissolution medium was 900ml of Gastric Simulated Fluid (without enzyme) pH 1.2 maintained at $37^0C \pm 1^0$ C. The paddle was rotated at 50 rpm for 20 min. The sample of 10ml was withdrawn after every 5 min. and its absorbance was measured at 248nm. Dissolution study of tablets revealed that more than 90% of drug released within 15 min. (Figure 5)

Taste evaluation by panel method:

Taste evaluation revealed that indion 204 masks the bitter taste of the drug completely.

Conclusion:

Use of cation exchange resin offers good method for preparing taste-masked substrate of ondansetron hydrochloride. Results obtained in this work show that drug-resin

complex effectively masked bitter taste of ondansetron HCL. Thus, complexation of ondansetron HCL with Indion 204 increases acceptability and palatability of formulated rapid disintegrating tablets. The results of this study can also be extrapolated to other intensely bitter drug by suitable selection of resin.

References:

[1] Bi Y., Sunada H., Yonezawa Y., Danjo K.and Lida K., "Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity", Chem. Pharm. Bull. 1996,44, 2121-2127

[2] Bruk,G.M.; Mendes,R.W. and Jambhekar,S.S.; Drug. Dev. Ind.Pharm, 12,1986 712-732.

[3] Sohi H, Sultana Y, Khar RK. Taste masking technologies in oral pharmaceuticals: recent

[4] developments and approaches. Drug Dev Ind Pharm 2004; 30:429-48.

[5] Mahesh Bhalekar, J.G.Avari and S.B. Jaiswal; "Cation Exchangers in pharmaceutical formulations." Indian Journal of pharmaceutical Education,38(4), Oct –Dec. 2004.

[6] Borodkin, S. sunderberg, "Polycarboxylic acid Ion Exchane Resin absorbates for taste coverage in chewable tablets," Journal of Pharmaceutical Science, 60(10), PP 1523-1527,(1971).

[7] Sambhaji Pisal, Ranna Zainnudin, Praddin Nalawade, Kakasaheb Mahadik and Shivajirao Kadam. " Molecular properties of ciprofloxacin Indion 234 complexes",AAPS Pharm. Sci.Tech 2004 ; 5(4) Article 62.

[8] European patent 0501763(1992).

[9] Manek, S.P.; Kamat,V.S.; Indian Journal of Pharmaceutical Science; 43, PP 209-212(1981).

[10] Kalmen, C. and Kressman,T.R.;Ion Exchange in Organic and Biochemistry, New York: Wiley interscience, 1957,502.

[11] Jain, N.K.; Advances in controlled and novel drug delivery; First edition PP 290 (2001).

[12] Bruck, S.D.; Controlled drug delivery; Vol –I, PP 150-151.

[13] Indurwade N.H. , Rajyaguru T.H. and Nakhat P.D.; "Novel approach- Fast Dissolving Tablets", Indian Drugs, 2002,39(8), PP 405-409

[14] Sastry S.V., Nyshadam J.R.and Fix J.A. " Recent technological advances in oral drug delivery- A Review", Pharm. Sci.Tech.Today, 2000, PP 138-144

[15] Grother, L.P., et.al; " Taste masked fast dissolved freeze dried tablets" Cardinal Health, Pharmaceutical Technology and services.

[16] Kaushik, D., Dureja, S. and Saini T.R. "Mouth Dissolving Tablets- A Review", Indian Drugs, 41(4), PP 187-193. April 2003.