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Formulation and Evaluation of Taste Masked Fast Disintegrating Tablet of Tramadol HCl

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ABSTRACT

Orally disintegrating tablet are gaining popularity over conventional tablets due to their convience in administration and suitability for patients. The purpose of the research was to mask the intensely bitter taste of tramadol hydrochloride and to prepare orally disintegrating tablets for achievement of quick onset of action of the drug. Tramadol hydrochloride is an analgesic which has been prove to be efficient in managing relief from pain and including pain after surgery. In the present study an attempt has been made to prepare bitter less orally disintegrating tablet of tramadol hydrochloride using Eudragit EPO as a taste masking agent. Direct compression method was used for preparing tablet & super disintegrating agent like Crosspovidone, Crosscarmellose sodium and sodium starch glycolate were used to prepare blend and evaluated for pre-compression parameter such as bulk density, compressibility, and angle of repose etc. the prepared batches of tablets were evaluated for hardness, weight variation, friability, drug content, disintegration time and in-vitro dissolution profile was found to be satisfactory. It was found that Eudragit EPO being hydrophilic facilitated the increase in the uptake of the saliva thus showing the complimentary action of that superdisintegrant.

Keywords: Tramadol hydrochloride, superdisintegrant, orally disintegrating tablet, Eudragit EPO.

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INTRODUCTION

The bitter taste of the drugs which are orally administered often contributes to patient non-compliance in taking medicines, especially for children and elderly [1]. Unfortunately, majority of the drugs have a natural bitter taste that can create a burning feeling in the throat or in the mouth. In particular, a bitter taste can decrease the patient compliance and thus reducing an effective pharmacotherapy. In order to achieve an acceptable palatability, the addition of flavors or sweeteners is limited and may not be efficient enough to mask the taste buds of drugs and requires the use of technological processes [2]. A number of taste masking approaches like the use of ion exchange resins [3], the use of inclusion complexes with cyclodextrins[4], viscosity modifications [5], granulation and melt granulation[5] have been described. More than 50 percent of pharmaceutical products are orally administered for several reasons and undesirable taste is one of the important formulation problem encountered with such oral products[7]. The taste of a pharmaceutical product is an important parameter for governing compliance. Thus, taste masking of oral pharmaceuticals has become an important tool to improve patient compliance and the quality of treatment especially in pediatrics. Therefore, formulation of taste masked products is a challenge to the pharmacists[8-9]. 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 various dosage forms developed to improve the ease of administration, the oral disintegrating tablet (ODT) is the most widely preferred commercial products[10-11]. The ODT has remarkable disintegration properties; it can rapidly disintegrate without water in the mouth within a few seconds. When an ODT is placed in the oral cavity, saliva quickly penetrates into the pores causing rapid disintegration[12]. The ODT presents considerable advantages for the patient (or elder) who cannot swallow (Dysphasia), or who is not permitted water intake because of disease. Such tablets can be produced by various methods; Namely, 1) drying after filling the pockets of the press through pack (PTP) with dispersed solution of the drug, 2) drying after low-pressure compression of humid powder granules containing the drug, 3) compression of dry powder granules containing the drug and, shaping by direct compression after mixing excipients and the drug. [13]. Granulation is process of size enlargement where small particles are gathered into larger aggregates intended for compression into tablets. Following are some reasons for performing granulations [14]

- Increase flow property which required producing consistent weight and uniform strength

- Increase Compressibility which is essential to form stable, intact and compact mass when pressure is applied
- Improve Appearance, mixing properties, to avoid dustiness.
- Moreover, granulations prepared by spray granulation are devoid of the unpleasant taste of drug probably due to coating of polymer on drug. Taste of API masked using strong polymer (binders) forming a film on API Thus the first part of our study consisted of the preparation of taste masked granulate of Tramadol HCL Thereafter, the second part of the study encompassed the preparation of tablets to evaluate the potential of compressing prepared taste masked granulate using different excipient. The potential of flavoring agent and taste masking flavor was also evaluated. Finally, the technological characteristics of the prepared tablets were evaluated in order to find the formula with the least time of disintegration and friability and eventually the best hardness.

Methods of Taste Masking

1) Taste masking with flavors, sweeteners & amino acids.
2) Polymer coating of drug.
3) Formation of Inclusion complexes.
4) Ion- exchange resin complex.
5) Solid dispersion. Microencapsulation.
6) Mass extrusion.
7) Multiple emulsions.
8) Development of liposome.
9) Prodrug concept.
10) Spray drying technique.
11) Adsorption
12) By using lipophilic vehicles like lipids & lecithin's.
13) Formation of salt or derivatives.
14) Use of amino acids and protein hydrolysates.

MATERIAL AND METHOD:

Tramadol HCL was a gift from Glenmark pharmaceuticals (Mumbai). Eudragit EPO was a gift from Evonik Degussa Mumbai. Mannitol, Avicel 101 (microcrystalline cellulose), Avicel 112 [low moisture content microcrystalline cellulose] and Prosolv SMCC 90 [silicified microcrystalline cellulose] were provided as gift samples by Signet chemicals. Flavors and taste masking flavor of

Firmenich were provided by Manish global. All other chemicals used in the study were of analytical grade.

Preparation of Tramadol HCL taste masked granulate

Inclusion complex of Tramadol HCl and Eudragit EPO were prepared by kneading method. Kneading method was selected as it is simpler and less time consuming than the solvent evaporation method. Tramadol HCl and Eudragit EPO were weighed separately in 1:1 molar ratios. Thick slurry of Eudragit EPO in water was prepared. Tramadol HCl was added to it in small quantities while continuous kneading. Kneading was continued for 3 hr and the complexes were evaluated for taste masking.

Characterization of DRC (Drug Polymer Complex) In Vitro Taste Evaluation

A panel of ten healthy human volunteers was selected for the study. Each volunteer held a quantity of DRC equivalent to 50 mg of Tramadol HCl in oral cavity for 30 seconds. The taste of the DPC was reported by them immediately, then after 30, 60, 120, 180 and 300 seconds on the scale described earlier.

Determination of threshold bitterness concentration of Tramadol Hydrochloride

Threshold bitterness concentration is the minimum concentration at which bitterness starts to appear and continues to provoke after 30s. Most of the volunteers rated 20 µg/ml as the threshold bitterness concentration for Tramadol Hydrochloride (Table 1). It was concluded that the taste masked form of the drug should not release more than or equal to 20 µg/ml of the drug in mouth within 2 minutes for satisfactory taste masking.

Table 1: Rating by the volunteers for different solutions of Tramadol Hydrochloride on the scale of bitterness(0: no bitterness, 1: threshold bitterness, 2: bitter, 3: moderate bitterness and 4: strong bitterness)

Volunteer No.	Rating on the scale of bitterness				
	10µg/ml	20µg/ml	30µg/ml	40µg/ml	50µg/ml
1.	0	0	1	1	2
2.	0	1	2	2	3
3.	1	1	2	2	3
4.	0	1	2	2	3
5.	0	1	1	2	3
6.	0	1	2	3	3
7.	0	1	2	2	3
8.	0	0	1	1	2
9.	0	1	2	2	3
10.	0	1	1	2	3

Formulation of Oral Disintegration Tablets

Direct Compression Method was used to prepare the ODT of Tramadol HCL Eudragit EPO Complexes. Different Excipients are incorporated are mannitol. Avicel pH (as diluents). Aerosil (as lubricants) and asparatame (as sweetener) Superdisintegating such as Crosscarmallose sodium, Cross Povidone . Sodium Starch glycolate were used in different concentration [20,21]

Table 2.Composition of fast disintegration tablets of Tramadol HCL

Ingradients	F1	F2	F3	F4	F5	F6	F7	F8	F9
DPC* eq.to.100mg	100	100	100	100	100	100	100	100	100
MCC*	30	30	30	30	30	30	30	30	30
SSG*	6	9	12	-	-	-	-	-	-
CCS	-	-	-	6	9	12	-	-	-
CP*	-	-	-	-	-	-	6	9	12
Mannitol	160.28	157.28	153.28	160.28	157.28	153.28	160.28	157.28	153.28
SIO_2*	3	3	3	3	3	3	3	3	3
ASP*	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12
Menthol	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Mint flavour	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

DPC-Drug polymer complex(Tramadol HCL +Eudragit EPO), MCC –Microcrystalline cellulose , SSG-Sodium starch glycolate, CCS-Cross cramalose sodium , CP-Cross povidone, SIO_2-Silcon dioxide, ASP-Aspartame(Sweeting agent), Mannitol(diuent for direct compression

Evaluation of Tablets

Hardness

Five tablets from each batch were selected and hardness was measured using hardness tester to find the average tablet hardness.

Friability(%F)

Twenty tablets from each batch were selected randomly and weighed. These tablets were subjected to friability testing using Roche friabilator for 100 revolutions. Tablets were removed, de-dusted and weighed again

Weight variation

Weight variation was calculated as per method descried in USP Pharmacopoeia. 20 tablets were weighed individually and the average weight is calculated. The requirements are met if the weights of not more than 2 of tablets differ by more than the percentage listed in Table and no tablets differ in weight by more than double that percentage.

Uniformity of content

Five tablets were selected randomly and powdered. A quantity of this powder corresponding to 50 mg of Tramadol was dissolved in 100 ml of 0.1 N HCl, stirred for 60 min and filtered. 1 ml of the

filtrate was diluted to 100 ml with 0.1 N HCl. Absorbance of this solution was measured at 271 nm using 0.1 N HCl as blank and content of Tramadol was estimated.

Disintegration time

Many reports suggest that conventional DT apparatus may not give correct values of DT for FDTs. The amount of saliva available in the oral cavity is very limited (usually less than 6 ml) whereas the conventional DT apparatus uses a large amount of water with very rapid up and down movements. FDT is required to disintegrate in such small amount of saliva within a min without chewing the tablet. In a simplest method to overcome this problem, 6 ml of phosphate buffer of pH 6.8 was taken in a 25 ml measuring cylinder. Temperature was maintained at 37±2°C. A FDT was put into it and time required for complete disintegration of the tablet was noted.

Dissolution studies

Dissolution test was carried out using USP Type II dissolution test apparatus at 37±2°C and 50 rpm speed. 900 ml of 0.1 N HCl was used as dissolution medium. Aliquot equal to 5 ml was withdrawn at specific time intervals & amount of Tramadol HCl released from tablets was determined.

RESULTS AND DISSUCTIONS

1. Calibration curve of Tramadol hydrochloride

The absorbance was measured by spectrophotometer at 271 nm using 0.1 N HCL.

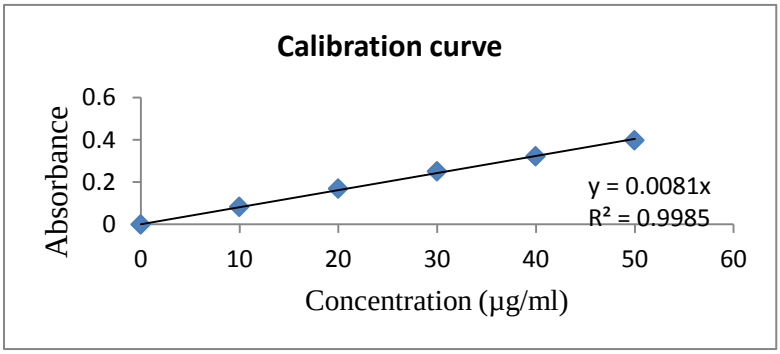

Figure 1:- Standard Calibration Curve of Tramadol Hydrochloride.

Table 3. Observations for standard curve of Tramadol Hydrochloride in 0.1 N HCL.

Sr. No.	Concentration of drug in µg/ml	Absorbance
1	0	0
2	10	0.083
3	20	0.169
4	30	0.25
5	40	0.322
6	50	0.397

Infrared Spectroscopy Study

The IR technique was used for identification of Tramadol HCl.

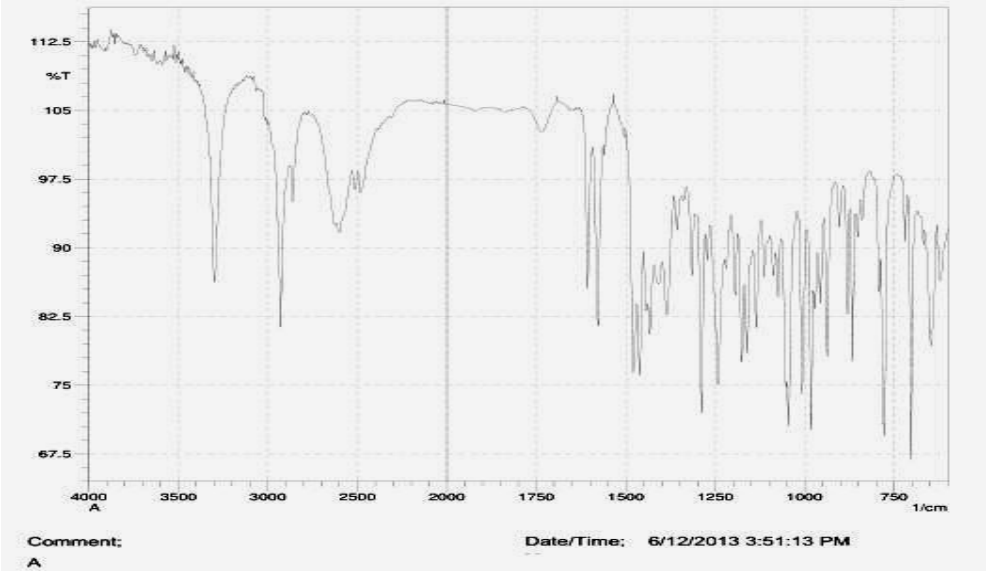

Figure 2: IR spectra of Tramadol HCl

The FT-IR spectrum of Tramadol Hcl (API), the peaks at following values which are characteristic of the drug:

Table.4 :-Interpretation of FTIR spectrum of Tramadol HCL

Wave length cm^{-1}	% T	Interpretation
3301.91	64	C-N stretch
2931.6	65	C-H Stretching
1604.66	78	Hydro halide salt associated with tertiary amines
1384.79	74	O-H stretch
1242.07	70	C-O stretch

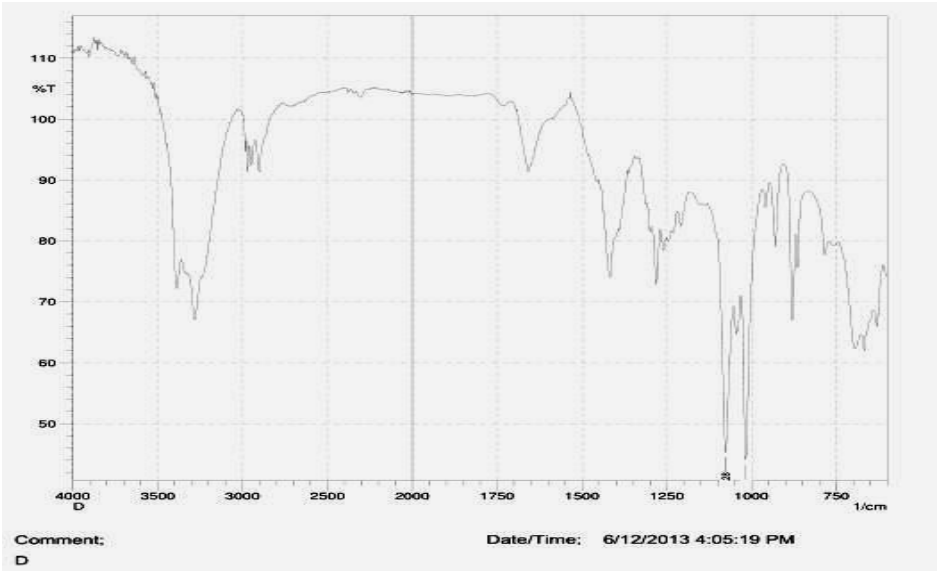

Figure 3 :IR spectra of Formulation

Table.5:-Interpretation of FTIR spectrum of Formulation

Wave length cm^{-1}	% T	Interpretation
3388.01	79	O-H stretch
2915.6	93	C-H Stretch
1645.88	95	H-O-H stretch
1155.19	80	C-O stretch
1008.07	55	C-O-C stretch

DSC studies (Differential Scanning Calorimetric)

The thermogram of Tramadol HCl shows a sharp endothermic peak at 198.82°C corresponding to melting of pure drug and its crystalline nature,

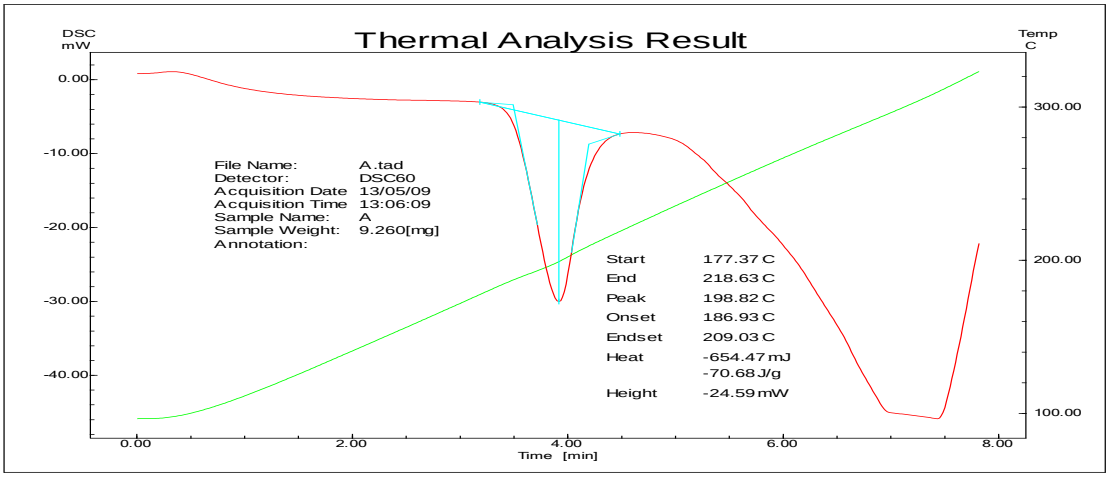

Figure.4:-Differential Scanning Calorimetry study of Tramadol HCl.

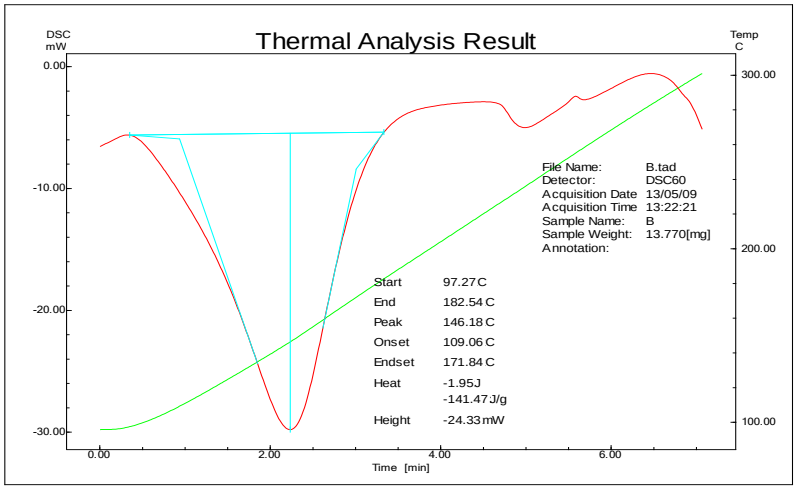

Figure.5:-Differential Scanning Calorimetry study of Formulation

Micromeritics Properties;

All the formulation blend was prepared by the by geometric mixing. The angle of repose of all batches shows in the range of 23 to 29^0 which indicates that blend has good flow property. Also

the compressibility index and Hausner's ratio was calculated, the figures showed that blend has good flow property

Table 6: Preformulation study of Fast Disintegration Tablets prepared by Direct Compression Method.

Formulation Code	Bulk density (gm/ml)±SD	Tapped Density (gm/ml)±SD	Hausner ratio	Compressibility index	Angle of repose
F1	0.8294±0.02	0.9296±0.03	1.2389	19.28	27.78±0.03
F2	0.8626±0.03	0.9036±0.04	1.2173	17.85	28.08±0.02
F3	0.8439±0.04	0.9156±0.01	1.1666	12.85	26.06±0.04
F4	0.8321±0.02	0.9221±0.02	1.1764	15.00	24.67±0.01
F5	0.8284±0.02	0.9286±0.04	1.1382	12.14	25.55±0.02
F6	0.8675±0.02	0.9135±0.02	1.1200	10.71	27.08±0.01
F7	0.845±0.02	0.9916±0.01	1.111	10.00	25.06±0.01
F8	0.864±0.02	0.9234±0.04	1.0852	7.85	23.67±0.02
F9	0.8221±0.03	0.9247±0.02	1.0769	7.14	24.85±0.01

Post Compression Evaluation Parameters of Formulated ODT

The tablets blend of all the batches was evaluated for different derived properties like angle of repose, bulk density, compressibility index, indicated that the flow ability of blend is significantly good.

Table 7. Physical evaluation of Fast Disintegration Tablets of Tramadol Hydrochloride

Formulation Code	Weight Variation (mg)±SD	Hardness (kg/cm^2) ±SD	Thickness (mm) ±SD	Disintegration Time (s) ± SD	Friability ± SD%	% Assay ± SD
F1	300.31 ± 1.61	2.9± 0.23	2.6 ± 0.02	78±1.02	1.02±0.02	98.64±1.02
F2	300.19 ± 1.32	3.0± 0.52	2.8 ± 0.03	69±0.89	0.88±0.01	99.21±1.26
F3	300.42 ± 1.47	3.2± 0.29	2.9 ± 0.04	60±1.21	0.8±0.04	99.42±0.85
F4	299.92 ± 1.46	3.0± 0.52	2.8 ± 0.02	66±0.67	0.73±0.02	98.41±0.62
F5	300.89 ± 2.11	3.5± 0.59	2.6 ± 0.01	50±0.96	0.66±0.03	98.53±1.08
F6	300.33 ± 1.68	3.5± 0.76	2.7 ± 0.02	45±0.82	0.60±00.02	98.02±0.96
F7	301.06 ± 1.20	3.5± 0.72	2.9 ± 0.05	36±0.69	0.54±0.01	97.93±1.21
F8	299.86 ± 1.42	3.5± 0.53	2.9 ± 0.03	20±0.77	0.48±0.03	99.78±1.05
F9	300.63 ± 1.63	3.6± 0.28	2.8 ± 0.04	31±0.81	0.41±0.01	99.23±0.85

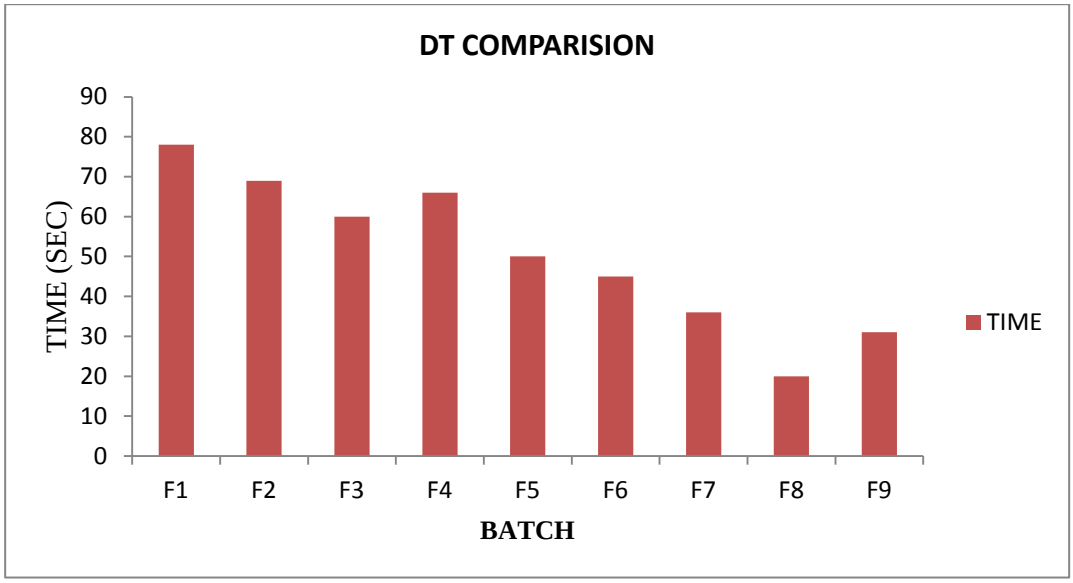

Figure.6:- Disintegration Time comparison

In vitro drug release:

Dissolution rate was studied by using USP type-II apparatus at 50 rpm using 900 ml of 0.1N HCl solution as dissolution medium. Temperature of the dissolution medium was maintained at 37 ± 0.5^0C, aliquot of dissolution medium was withdrawn at every 5 min interval. The absorbance of filtered solution was measured by UV/ VIS spectrophotometric method at 271 nm and concentration of the drug was determined from standard calibration curve. The cumulative % drug release is shown in following table.8.

Table.8: In vitro Drug Release profile for Batch F1 to F9.

Sr,no	Time	% Drug Release								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0	0
1	5	78.17	81.71	77.47	75.78	78.52	81.46	76.27	82.46	78.52
2	10	94.43	95.83	95.08	92.24	96.28	96.03	94.34	97.48	95.63
3	15	96.68	98.03	97.68	93.39	97.08	97.33	95.58	97.75	95.78
4	20	96.90	98.28	97.98	94.44	97.18	98.28	95.73	98.38	96.93
5	25	97.23	97.73	98.33	95.18	98.43	98.58	96.83	98.88	97.78
6	30	98.53	98.68	99.13	97.68	99.28	99.37	98.48	99.92	99.23

CONCLUSION:

All the tablet formulations disintegrated rapidly in vitro within 20-78 second. and but rapid disintegration and dispersion was observed in formulation F3,F5,F6,F8, and F9 .Thus a rapid disintegration of tablets in the oral cavity may be contributed to the use of superdisitegrants and formation of pores. This porosity may lead the saliva to penetrate into the tablets which further causes increased in the concentration of cross-povidone from 3 % causes increased in the

disintegration time whereas varying cross carmallose sodium concentration from 3 % did not appreciably affect the disintegration time. So it can be concluded that tablet containing 3 % cross-povidone could be considered as an optimum concentration which demonstrated excellent in-vitro disintegration power and also faster dissolution profile than those containing higher (up to 5%) concentration of cros-povidone.F8 formulation showed the maximum drug release i.e. 99.92 % than any other formulation. Hence we may concluded that F8 formulation which containing cross-povidone is the ideal superdisintegrant in the concentration of 3 %.It was found that Eudragit EPO being hydrophilic facilitated the increase in the uptake of the saliva thus showing the complimentary action of that superdisintegrant.

REFERENCES:

1. Roy GM. Taste masking in oral pharmaceuticals. Pharm. Tech 1994; Eur. 24–35.
2. Shimano K, Kondo O, Miwa A, Higashi Y and Goto S. Evaluation of uniform-sized microcapsules using a vibration-nozzle method. Drug Dev. Ind. Pharm 1995; 21: 331–347.
3. Lu MYF, Borodkin S, Woodward L, Li P, Diesner C, Hernandez L et al. A polymer carrier system for taste masking of macrolide antibiotics. Pharm. Res 1991; 8: 706–712.
4. Motola S, Agisim GR. Palatable ibuprofen solutions. 1991 US Patent 5,024,997.
5. Blase CM and Shaw MN. Aqueous pharmaceutical suspensions for pharmaceutical actives. 1993 EP application no. O556057 B1 to McNeil-PPC Inc.
6. Appelgren C and Eskilson C. Novel method for the granulation and coating of pharmacologically active substance. Drug. Dev. Ind. Pharm 1990; 16: 2345–2351.
7. Lachman, Liberman HA and Anig JL. Theory and practice of industrial pharmacy. 3rd ed. Mumbai: Varghese Publishing House 1991; 296-302.
8. Bi Y, Sunanda H, Yonezawa Y, Danjo K, Otsuka A, Iida K. Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity. Chem. Pharm. Bul (Tokyo) 1996; 44: 2121-2127.
9. Nanda AR and Kandarapu Garg S. An update on taste masking technologies for oral pharmaceuticals. Indian J Pharm Sci 1996; 64: 7-10.
10. Chang R, Guo X, Burnside B, Couch R. A review of fast dissolving tablets. Pharm Tech. (North America). 2000;52-58.
11. Bi Y, Sunada H, Yonezawa Y, Dayo K, Otsuka A, Iida K. Preparation and evaluation of a compressed tablet rapidly disintegrating in oral cavity. Chem Pharm Bull (Tokyo). 1996;44:2121-2127.

12. Watanabe Y, Ishikawa Y, Utoguchi N. Matsumoto M. Preparation and evaluation of tablets rapidly disintegrating in saliva containing bitter taste masked granules by the compression method. Chem. Pharm. Bull. 1999; 47:1451-1457.
13. Kaushik D, Dureja H, Saini TR. Mouth dissolving tablets: A review. Indian Drugs-Bombay. 2004; 41: 187-193.
14. "United States pharmacopoeia 24/ National Formulary 19", The Official Compendia of Standards. Asian ed. Rockville, MD. 1913-1914.
15. Ahire, S.B.; Bankar, V.H.; Gayakwad P.D.; Pawar S.P. ; A Review: Taste masking Techniques in Pharmaceuticals; Pharma Science Monitor: An International Journal of Pharmaceutical Science (2011); ISSN: 0976-7928; 1645-1646.
16. Lachman L., Liberman H. A., Kanig J. L. The theory and practice of industrial pharmacy. 3rd ed. Varghese Pubulication House, Mumbai. (2003) 293-294.
17. Brahmankar D. M., Jaiswal S. B. Biopharmaceutics & Pharmaceutics. 1st ed. Vallabh Prakashan, Delhi (1995) 335-371.
18. Cousin G, Bruna E, Gendrot E , US Patent No. US5464632,1995.
19. Kibbe A, In Handbook of Excipients, 3rd Edn The Pharmaceutical Press London 200, P. No 501