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Research Article

FORMULATION AND EVALUATION OF ORAL DISPERSIBLE TABLETS OF RIZATRIPTAN BENZOATE

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ABSTRACT

Oral dispersible tablets have emerged as an alternative to the conventional oral dosage formsto improve the patient compliance. Due to problem in swallowing ability with age, the pediatric and geriatric patients complain of difficulty to take conventional solid dosage forms. The ODT's are solid dosage forms that dissolve or disintegrate rapidly in the oral cavity. This results insolution or suspension without the need of water. The main objective of this work is to formulateand evaluate Rizatriptan Benzoate ODT's using different concentration of super disintegratingagents like croscarmellose, Sodium Starch Glycolate (SSG),Crospovidone. Tablets wereprepared by direct compression method and evaluated for hardness, thickness,uniformity of weight, friability,wetting time, disintegration time, percentage of drug release and assay by HPLC. Drug compatibility with excipients was checked by FTIR studies. No chemical interaction between drug and excepients was confirmed by FTIR studies. Moisture uptake studies and stability studies are also conducted. The results indicated that formulationprepared with Crospovidone was found to be optimised which provides maximum drug release(100%) and minimum disintegration time (less than 10 second). The drug release from all the formulations followed first order kinetics.Stability studies of the tablet at 40±2º/75%±5%RH for 3 months showed non-significant drug loss. Apart from fulfilling all official and other specifications, the tablets exhibited higher rates of release.

Keywords: Oral dispersible tablets, Rizatriptan benzoate, Crospovidone, Super disintegrant, Direct compression and Innovator.

INTRODUCTION

Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Orally disintegrating tablets offer an advantage for populations who have difficulty in swallowing. It has been reported that Dysphagia (difficulty in swallowing) is common among all age groups and more specific with paediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications.United States of America

Food and Drug Administration (USFDA) define ODTas "A solid dosage form containing medicinalsubstances or active ingredient which disintegratesrapidly usually within a matter of seconds whenplaced upon a tongue".The major advantage of the ODT formulationis that it combines the advantages of both liquid andconventional tablet formulations. It provides theconvenience of a tablet formulation, and alsoallowing the ease of swallowing provided by the liquid formulation. The various technologies usedto prepare ODT's include direct compression,sublimation, tablet moulding, spray drying, freeze drying and mass extrusion. The new generation anti-migraine drug,Rizatriptan benzoate is a potent and selective 5-hydroxy tryptamine 1B/1D receptor agonist and isconsidered more effective than the traditionaltriptans for the treatment of acute migraine attack.It is a faster acting oral triptan with the highest pain free and sustained pain free responses of the available triptans.The current commercially available ODT of Rizatriptan benzoate (MAXALT-MLT, USA) is prepared by lyophilization. However; the ODTsformed by lyophilization may have low mechanical strength and may exhibit-poor stability at highertemperatures and humidity.The present study is to formulate an oraldelivery device, in the form of rapidly disintegratingtablets by using direct compression technology, withthe aim of rapid disintegration and a complete drugrelease in a short period of time. In this study, efforthas been made to prepare different formulations based on varying concentrations of superdisintegrants at their two levels viz., higher and lowerconcentrations. The main effect and the interactionsof disintegrants on dispersion time and drug releasewere studied.

MATERIALS AND METHODS

Rizatriptan Benzoate was obtained as a gift sample from Natco Pharma Ltd, Hyderabad.Crospovidone XL,Croscarmellose sodium, Avicel pH 102 were obtained as a gift sample from Signet chemical corporation, Mumbai. Sodium starch glycolate andother excipients were obtained as a gift sample from KMV enterprises, Hyderabad. All other chemicalsused were of analytical grade.

Table 1: Formulation development for 10mg tablet

S. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Rizatriptan Benzoate	14.53	14.53	14.53	14.53	14.53	14.53	14.53	14.53	14.53
2	Spray dried Lactose	50.39	_	_	_	_	_	_	_	_
3	Avicel pH102	_	83.98	117.57	50.39	50.39	50.39	50.99	49.79	50.76
4	Pearlitol 200SD	117.57	83.98	50.39	117.57	117.57	117.57	118.97	116.17	118.45
5	Cross povidone	10	10	10	10	_	_	8	12	10
6	Cross carmellose sodium	_	_	_	_	10	_	_	_	_
7	Sodium starch glycollate	_	_	_	_	_	10	_	_	_
8	Aspartame	4	4	4	4	4	4	4	4	4
9	Peppermint flavour	1	1	1	1	1	1	1	1	1
10	Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	1.25
	Total weight(mg)	200	200	200	200	200	200	200	200	200

Manufacturing process

Formulation of oral disintegrating tablets of Rizatriptan 10mg were carried out by direct compression technique.Rizatriptan was weighed and sifted through #30 mesh and then taken in a polybag. Diluents were weighed according to ratio and sifted through #30 mesh and added to the above and mixed for 5 minutes. Superdisintegrant was weighed and sifted through #30 mesh and added to the above and mixed for 5 minutes Sweetener and flavor were weighed and passed through #30 mesh separately and added to the above mixture one after the other and for each addition the mixture was blended thoroughly for 5 minutesThe lubricant Magnesium stearate was weighed and sifted through #30 and added to the above mixture and blended with the mixture for 1 minute.The final blend was mixed thoroughly for 2-3 minutes in the poly bag and tablets were compressed as 10mg tablets using 8.5 mm round flat shaped punches.

Evaluation of powder blends

Bulk density

Apparent bulk density (ρb) was determined by placingpresieved drug excipients blend into a graduatedcylinder and measuring the volume (Vb) and weight(M) "as it is".

ρb = M/Vb

Tapped density

The measuring cylinder containing a known mass ofblend was tapped for a fixed number of taps. Theminimum volume (Vt) occupied in the cylinder and theweight (M) of the blend was measured. The tappeddensity (ρt) was calculated using following formula.

ρt = M/ Vt

Angle of repose

Angle of repose (α) was determined using funnelmethod. The blend was poured through a funnel thatcan be raised vertically until a maximum cone height(*h*) was obtained. The radius of the heap (*r*) wasmeasured and angle of repose was calculated.

α = tan -1 (*h/r*)

Compressibility index

The simplest way of measurement of free flowproperty of powder is compressibility, an indication ofthe ease with which a material can be induced to flowis given by % compressibility which is calculated asfollows:

C = (ρt – ρb) / ρt * 100

ρt - Tapped density, ρb - Untapped bulk density

Hausner's ratio

Hausner's ratio is an index of ease of powder flow; it iscalculated by following formula.

Hausner's ratio = ρt\ ρb

ρt - Tapped density, ρb - Untapped bulk density

Loss on drying (% LOD):

Loss on drying is an expression of moisture content. The loss on drying test is designed to determine the amount of water and volatile matters in a sample. when the sample is dried under specified conditions. The loss on drying of the blend (1g) was determined by using electronic lod (moisture halozen analyzer).

Evaluation of tablets

Thickness

Thickness was determined for randomly selected 20 tablets of each batch using a digital vernier scale and the average thickness was determined in mm. The tablet thickness should be controlled within a ± 5% variation of a standard.

Weight Variation

20 tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated. The tablets meet the USP specifications if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limits.

Hardness Test

The crushing load which is the force required to break the tablet in the radial direction was measured using a schluenzier hardness tester. The hardness of 10 tablets was noted and the average hardness was calculated. It is given in kp or kg/cm^2.

Percentage Friability

In friability testing the tablets are subjected to abrasion and shock. It gives an indication of the tablets ability to resist chipping and abrasion during transportation and shipping. If the tablet weight is ≥ 650 mg 10 tablets are taken and initial weight was noted. The tablets were rotate in the Roche friabilator for 4 minutes which gives 100 revolutions at 25 rpm. The tablets were dedusted and reweighed. For conventional tablets the percentage friability should be less than 1% where as friability values of up to 4% are acceptable for oral disintegrating and chewable tablets.

The percentage friability is expressed as the loss of weight and is calculated by the formula:

$$\% \text{ Friability} = \frac{\text{(Initial weight of tablets - Final weight of tablets)}}{\text{Initial weight of tablets}}$$

Disintegration Time

Disintegration time is the time taken by the tablet to break into smaller particles. The disintegration test is carried out in an apparatus containing a basket rack assembly with six glass tubes of 7.75 cm length and 2.15 mm in diameter the bottom of which consists of a 10 mesh sieve. The basket is raised and lowered 28-32 times per minute in the medium of 900 ml which is maintained at 37±2^{0}C. Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments through the sieve (# 10) was considered as the disintegration time of the tablet.

Table 2: Table Shows Evaluations Powder Blend

S. No.	Formulation Code	Bulk density (g/ml)	Tapped density (g/ml)	Carr'sindex	Hausners ratio	Angle of repose (θ)	%LOD
1	F1	0.58+0.02	0.79+0.02	26.58+0.03	1.36+0.04	25 +0.02	0.82+0.36
2	F2	0.68+0.04	0.76+0.01	13.1+0.03	1.11+0.04	26+0.04	1.06+0.41
3	F3	0.67+0.03	0.78+0.02	12.8+0.01	1.16+0.03	28+0.01	0.96+0.58
4	F4	0.59+0.01	0.65+0.03	9.2+0.04	1.10+0.01	24+0.02	0.88+0.37
5	F5	0.62+0.01	0.70+0.03	11.4+0.03	1.12+0.02	27+0.03	0.62+0.02
6	F6	0.59+0.04	0.66+0.04	10.6+0.02	1.11+0.03	25+0.01	1.15+0.51
7	F7	0.63+0.03	0.71+001	11.2+0.03	1.12+0.01	27+0.04	1.1+0.40
8	F8	0.66+0.02	0.73+0.01	9.5+0.01	1.10+0.04	24+0.02	1.03+0.34
9	F9	0.66+0.01	0.74+0.02	10.8+0.02	1.12+0.03	32+0.03	1.08+0.40

The time for disintegration of ODTs is generally <1min and actual disintegration time that patience can experience ranges from 5 to 30s.

Dissolution Studies: By (Uv Method)

Dissolution is a process by which the disintegrated solid solute enters the solution. The test determines the time required for a definite percentage of the drug in a tablet to dissolve under specified conditions.

The dissolution test was carried out in USP apparatus Type II (paddle) with water as the dissolution medium. The samples were drawn at 5, 10, 15. Fresh volumes of the medium were replaced with the withdrawn volume to maintain the sink conditions. Samples withdrawn were analyzed for the percentage of drug released.

Percentage water content by (KARL FISCHER TITRATION)

Transfer 35-40ml of a mixture of methanol to the titration vessel and titrate with karlfischer reagent to the electrometric end point, To consume any moisture that may be present (disregand the volume consumed, Since it does not enter into the calculation) use powder from 5 tablets ground to a fine powder in a atmosphere of temperature and releative humidity known not to influence the results. Accuracy weigh and transfer about 300mg of powder into the titration vessel.Mix and titrate with the karl fischer reagent to the electrometric end point. Calculate the watercontent of the specimen in mg taken by the formula.

S×F×100 ÷W

S= The volume in ml of reagent consumed in the titration

F= is the water equvivalence factor of the karl fischer reagent

W= wt of sample

Water Absorption Ratio

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed.

Water absorption Ratio = Finalweight /-Intial weight/Final weight x 100

Wetting Time

Wetting time is closely releated to the inner structure of the tablets and to the hydrophilicity of the excipient. It is obvious that pore sizes become smaller and wetting time increase with an increase in compression force or a decrease in porosity. A piece of tissue paper folded double was placed in a petriplate containing 6ml of water containing water soluble eosin dye. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds.

Wetting volume

The tablet is placed in the center of the petridish and with the help of 5ml pipette,distilled water was added dropwise on the tablet. The volume required to completely disintegration of the tablet was noticed as the wetting volume.

Assay By Hplc

Sample preparation

Equivalent to 50 mg of rizatriptan Benzoate was taken in 100 ml volumetric flask and 60ml of diluents was added and sonicated for 20 min. To this solution diluents was added upto the mark. Centrifuge at 300 rpm for 15 min, filter through pvdf filter. Take 3 ml of filtered solution and add 50 ml of diluent(30ppm).

Procedure

Separately injected equal volumes (about 10 µl) of diluents as blank and standard preparation and sample preparations into the system and the chromatograms were recorded and the peak area responses were measured and the percentage content of the drug in the sample was determined using the formula

$$\% \text{ Content of Rizatriptan} = \frac{TA \times SW \times 10 \times 100 \times P \times Avg\ wt}{SA \times 100 \times 100 \times TW \times 100 \times LA}$$

Moisture Uptake Studies

Moisture uptake studies for ODT should be conducted to have an insight into the stability of the formulation, as several excipients used are hygroscopic.Moisture uptake studies were carried out by weight method.Cleaned and dried petriplates were taken and their empty weights were recorded.10 tablets were placed into each petriplates and the total weight of each petriplate with the test substance was recorded.Finally the petriplates were placed in desicators saturated to 29, 43 and 75% relative humidities at 25 ^{0}C using various standard solutions.The weights of all the petriplates were recorded at the end of 1, 2, 4, 5, 6, 8, 24, 48, 72 hr.The petriplates were carefully wiped with tissue paper to remove any adhering moisture before the weight was recorded.

The percentage of moisture absorption was determined using the formula

$$\% \text{ Moisture absorption} = \frac{(\text{Observed weight} - \text{Initial weight})}{\text{Initial weight}}$$

Stability Studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity etc.

Objective

To generate documented evidence that the tablets manufactured comply with the finished product specifications under accelerated and long term stability conditions.

Design Plan

Accelerated study: The product is subjected to accelerated stability studies at 55 ^{0}C for 2 weeks and 40^{0}C±2^{0}C / 75% ±5% RH for six months.

Long term study: The product is subjected to long term studies at 25^{0}C±2^{0}C / 60% ±5%RH for 12 months.

Package type

The tablets were packed as 30's count in HDPE containers, induction sealed with adsorbent cotton.

RESULTS AND DISCUSSION

For each designed formulation, blend of drug andexcipients was prepared and evaluated formicromeritic properties shown in Table-2. Bulkdensity was found to be between 0.58±0.02 and 0.68±0.04 gm/cm3 and tapped density between0.66±0.04 and 0.79±0.02 gm/cm3 for allFormulations. From density data cars indexwas calculated and was found to be between 9.2±0.04and 26.58±0.03. Angle of repose was found to be in therange of 24.13±0.02 and 32±0.03. Hausner ratiowas found below 1.36. All the formulation shows thegood blend properties for direct compression andhence tablets were prepared by using direct compression technology.As the tablet powder mixture was free flowing, tabletsproduced were of Hardness (1.12- 2.08 kp) andfriability loss (0.21-1.29 %) indicated that tabletshad a good mechanical resistance. Drug content wasfound to be high (≥99.8%) in all the tabletformulations. Thus wetting times of tablets was foundto be crospovidone ≤ croscarmellose sodium ≤sodiumstarch glycolate. While dispersion time was foundcroscarmellose sodium ≤ sodium starch glycolate ≤crospovidone. The influence of superdisintegrants onthe dissolution of rizatriptan from the tablets isshown as below. The drug release in 5 min and 15 minincreased with increase in the level of crospovidone. However values decreased with increase inthe level of sodium starch glycollate. While values didnot change proportionally with increase in the level ofcroscarmellose shown in fig 1, 2 and 3. Out of nineformulations F4 formulation is best shows drugrelease 100 in 15 min shown in fig 2.Moisture uptake studies for the final batch F4 were performed at 43, 64 and 75% RH and there was a slight moisture uptake observed in tablets at 75% RH. The reproducibility batch F4 was loaded for long term and accelerated stability studies at 25 ± 2C/60±5% RH and 40±2C/75±5% RH. The results of stability data for 1st, 2nd month and 3rd months (40±2C/75±5% RH) were found to be good.

Table 3: Table Shows Evaluations of Tablets

Formulation Code	Average weight (mg)	Thickness (mm)	Hardness (kp)	Percentage Friability (%)	Disintegration Time (sec)
F1	199.23+ 0.12	2.97+0.02	1.12+0.12	1.29+0.06	11+0.44
F2	200.01+0.12	3.01+0.01	2.08+0.21	0.21+0.12	21+0.14
F3	200.03+0.24	2.89+0.04	1.77+0.23	0.39+0.11	13+0.25
F4	199.89+0.23	2.94+0.02	1.76+0.08	0.35+0.04	11+0.14
F5	200.01+0.27	3.01+0.02	1.78+0.14	0.43+0.12	14+0.36
F6	200.12+0.21	2.99+0.01	1.80+0.18	0.42+0.02	15+0.14
F7	199.98+0.16	3.03+0.03	1.76+0.16	0.40+0.04	14+0.12
F8	200.00+0.17	3.00+0.01	1.75+0.14	0.39+0.08	10+0.23
F9	200.02+0.22	3.01+0.07	1.74+0.22	0.39+0.12	12+0.36

Table 4: Dissolution Studies for Rizatriptan Odt

S. No.	TIME(min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0	0	0	0	0	0	0	0	0
2	5	87.3 + 0.034	89.5+ 0.05	89.9+ 0.024	90.1 + 0.031	90.2+ 0.032	89.3+ 0.06	89.7+ 0.026	89.8+ 0.036	89.7+ 0.024
3	10	94.5+ 0.023	96.1+ 0.032	95.9+ 0.026	97.3 + 0.031	96.1+ 0.05	96.9+ 0.012	96.8+ 0.026	97.4 + 0.05	97.0+ 0.031
4	15	99.0+ 0.05	99.2+0012.	99.7+ 0.06	100.0+ 0.015	99.3+ 0.12	99.8+ 0.05	99.9+ 0.03	100.1+ 0.06	99.7+ 0.024

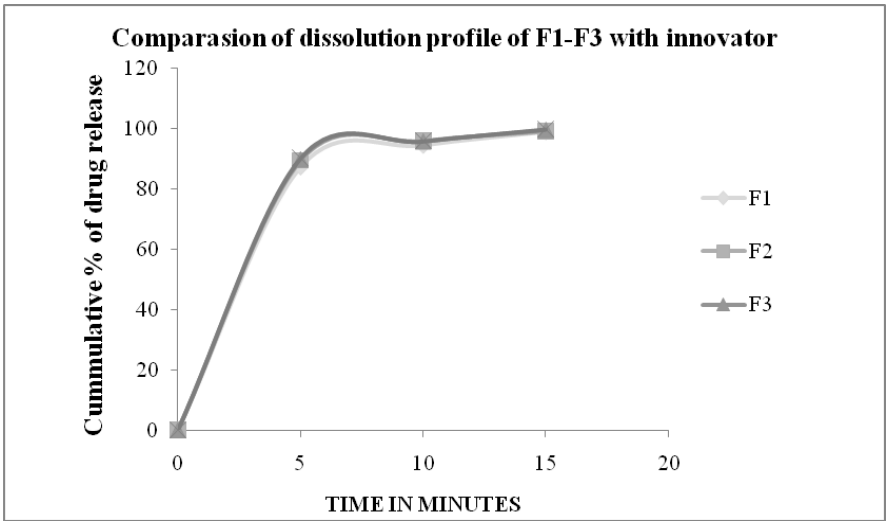

Fig. 1: Figure Shows % Cumulative Drug Release of Formulation F1, F2 and F3

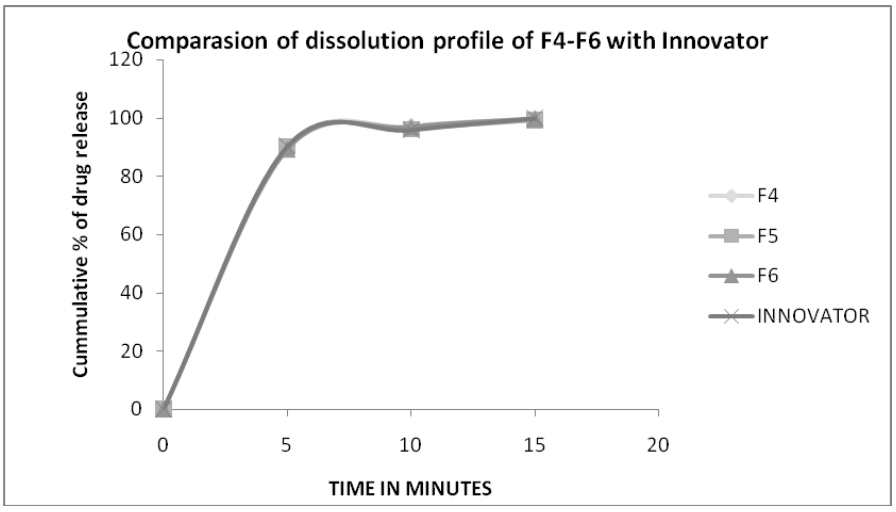

Fig. 2: Figure Shows % Cumulative Drug Release of Formulation F4, F5 and F6

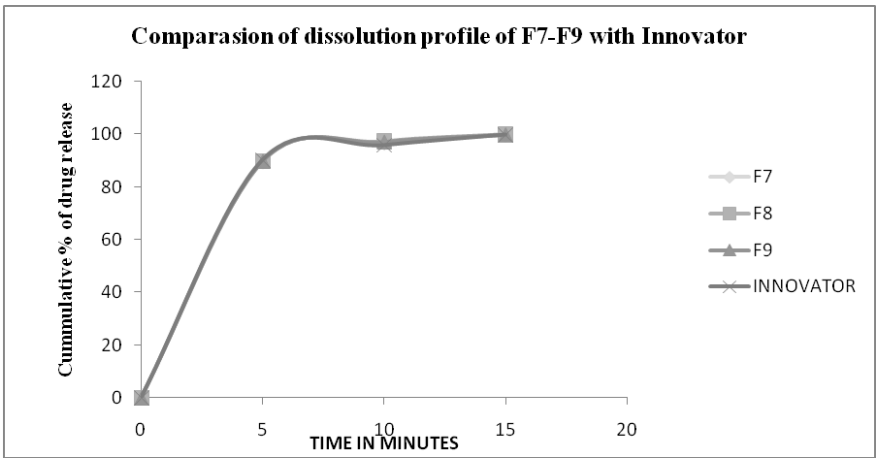

Fig. 2: Figure Shows % Cumulative Drug Release of Formulation F7, F8 and F9

CONCLUSION

Based on various studies carried out we have arrived at the following conclusions:

Direct compression can be used as a method for the preparation of oral disintegrating tablets of Rizatriptan.

Based on the preliminary studies various formulation trials (F1-F9) were carried out with different concentrations of superdisintegrants, diluents and lubricant. From the various formulations, the Formulation F4 was finalized as the optimized formula. Based on the various parameters which were compared with the reference.

Formulation F4 showed satisfactory results with various physicochemical evaluation parameters like Hardness, Percentage weight loss, Disintegration time, Dissolution profile, Assay and Moisture content when compared with the marketed product. When subjected to accelerated stability studies the tablets were found to be stable.

REFERENCES

1. Abhay Gupta, Robert Hunt, RakhiShas, VilayatSayeed, Mansoor Khan Disintegration of HiglySoluable Immediate Release Tablets: a Surrogate for Dissolution AAPS *PharmSciTech*,, Jun 2009,Vol 10: 2 .10.1208/s12249-009-9227-0
2. Adel M, Aley M, Semreen, Mazin K, Qato. To produce rapidly disintegrating Tenoxicam tablet via Camphor sublimation. Pharmaceutical Technology 2005.
3. Ansel's Pharmaceutical Dosage Forms And Drug Delivery Syatems, 8th edition 227-260
4. Aulton's Pharmaceutics, The design And Manufacture of Medicines, Biopharmaceutics and Pharmacokinetics, A Treatise, 2nd edition valabhPrakashan 315-384
5. Aurora J, Pathak V. Oral disintegrating technologies: Oral disintegrating dosage forms: An overview. *Drug Delivery Technology*. 2005; 5(3): 50-4.
6. B.G.Shiyani, R.B. Dholakiyal, B.V. Akbari, D.J. Lodhiyal, G.K. Ramani, Development and Evaluation of Novel Immediate Release Tablets of Metoclopramide HCl by direct compression using treated gellan gum as disintegration-accelerating agent. *Journal of Pharmacy Research* 2009 2(9),1460-1464
7. Basani G, Reddy S, Somagoni J.M, Rao Y.M. Formulation & Evaluation of orally Disintegrating Tablets of Baclofen.*Journal of Global Pharma Technology* 2010;2(3):137-145
8. Bhupendra, Prajapathi.G, Bhaskar Patel. Formulation, Evaluation & optimization of orally Disintegrating Tablet of Piroxicam. *International Journal Pharm Tech Research* 2010;2(3):1893-1899
9. Brahmankar, suniljaiswal, Biopharmaceutics and pharmacokinetics a treatise:25
10. Chang RK, Guo X, Burnside BA, Couch RA. Fast dissolving tablets. *Pharm Technol* 2000;24:52-58.
11. Dali Shukla, Subhashis Chakraborty, Sanjay Singh, Brahmeshwar Mishra, Mouth Dissolving Tablets: An Overview of Formulation Technology. *Scientia Pharmaceutia.* 2009; 76; 309–326.
12. Dave Brown**.** Orally Disintegrating Tablets - Taste Over Speed. *Oral delivery.* Sept2003;3(6).
13. Dedhiya et al, "Lercanidine Immediate Release compositions" United States Patent Application 200600134212
14. Eriksson et al "New Oral Immediate Release dosage form" United States Patent Application20060034 911
15. Fast Dissolving Tablet: An Overview, Journal of Chemical and Pharmaceutical Research, 2009, 1(1): 163-177-
16. Forsman et al, Immediate release tablet, United States Patent 6521253
17. Guidance for Industry Immediate Release Solid Oral Dosage Forms Scale-up and Post approval Changes Chemistry, Manufacturing and Controls, *In Vitro* Dissolution Testing and *In Vivo* Bioequivalence Documentaion, Center for Drug Evaluation and Research(CDER) Nov 1995 CMC 5
18. Guidance for Industry, Dissolution Testing of Immediate Release Solid Oral Dosage Forms, U.S Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Aug 1997, (Internet) Gupta, AK Mishra, V Gupta, P Bansal, R. Singh, AK Singh, REVIEW ARTICLE, Recent Trends of Fast Dissolving Tablet: An Overview of Formulation Technology, *International Journal of Pharmaceutical & Biological Archives* 2010: 1(1): 1-10
19. *Hand book of excipients*; 2006: 5: 132-135, 211-213, 430-433,731-733, 800-801.