ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

Vol 7, Suppl 1, 2014

ISSN - 0974-2441

Research Article

FORMULATION AND INVITRO EVALUATION OF ATAZANAVIR ORAL DISINTEGRATING TABLETS

G. ARCHANA*[1], P. NARAYANA RAJU[1], G. NAGARJUNA REDDY[1]

Department of Pharmaceutics, K.L.R Pharmacy College, Paloncha, Khammam. Email: g.archanapharmapal@gmail.com.

Received: 1 January 2014, Revised and Accepted: 31 January 2014

ABSTRACT

Objective: In this present work oral disintegrating tablet of atazanavir were designed with a view to avoid the first pass effect and to improve the bioavailability of atazanavir.

Method: Total fifteen formulations were prepared using superdisintegrants like cross povidone, cross carmellose sodium and sodium starch glycolate at concentrations 5 – 15 %. For better mouth feel sweetening agents and flavouring agents were added. Oral disintegrating tablet of atazanavir were prepared by direct compression method.

Results: The prepared powdered blend of the formulations were evaluated for micromeritic properties like angle of repose, bulk density, tapped density, Hausner's ratio, Carr's compressibility index and results showed that the powder blend has good flow property. The prepared batches of tablets were evaluated for post compression parameters like weight variation, content uniformity, thickness, hardness, wetting time, in vitro disintegrating time and friability and the results were found to be uniform within the pharmacopoeial limits. Effect of superdisintegrants on in-vitro release of drug has been studied. Among the 15 formulations, tablets containing cross povidone (15%) showed excellent in-vitro disintegration time of 21 secs and complete drug release in 15 mins. FTIR & DSC studies confirmed that there is no evidence of interaction between the drug and superdisintegrants and the selected ingredients were compatible.

Conclusion: It is concluded that oral disintegrating atazanavir tablets could be prepared by direct compression using different concentration of superdisintegrants.

Keywords: Atazanavir, superdisintegrants, direct compression, oro disintegrating tablets.

INTRODUCTION

The main aim in formulating atazanavir oral disintegrating tablets is to avoid first pass effect of the drug as it gets extensively metabolized in the liver when ingested orally. Oral route is the most widely accepted route of administration, because of its advantages like convenience of self administration and easy manufacturing [1-2]. Over a decade, formulation of orally disintegrating tablets (ODTs) has gained enormous demand and has significant impact on the patient compliance. Oral dispersible tablets are appreciated by particularly a segment of people who have difficulty in swallowing [3]. ODT"s can be conveniently given to peadiatric geriatric population along with psychiatric patients and patients suffering with motion sickness, nausea and vomiting complications [4, 5, 6]. Orally disintegrating tablets can also called as fast disintegrating tablets, fast dissolving tablets, mouth dissolving tablets, orodispersible tablets, porous tablets, quick disintegrating tablets, rapid dissolving tablets, and rapimelts. United States pharmacopoeia (USP) approved these dosage forms as ODTs. Recently, European Pharmacopoeia has used the term orodispersible tablet for tablets that readily disperses within 3 min in mouth before swallowing [7].

United States Food and Drug Administration (FDA) defined ODT as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for ODTs generally ranges from few seconds to about a minute. [8]

Due to absorption of drugs in oral cavity when formulated as ODT, the bioavailability of drugs can be increased. Pregastric absorption of saliva containing dispersed drugs avoids first pass metabolism effect when compared to standard tablets that are meant to swallow [9-10].

ODT"s does not require water after oral administration and bitter drugs can be taste masked effectively rendering them to have pleasant mouth feel [11].

Atazanavir is an antiretroviral drug of protease inhibitor class, used to treat human immunodeficiency virus (HIV). Atazanavir can be given once-daily and is reported to have lesser effects on the patient's lipid profile - the amounts of cholesterol and other fatty substances in the blood. Like other protease inhibitors, it can also be given in combination with other HIV medications.

Atazanavir acts by selectively inhibiting the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells by binding to the active site of HIV-1 protease. This prevents the formation of mature virions. But atazanavir is not active against HIV-2. Atazanavir gets extensively metabolized in humans, primarily in the liver. Monooxygenation and dioxygenation are the major biotransformation pathways of atazanavir in humans. Atazanavir is rapidly absorbed and has T_{max} of approximately 2.5 hours. It has been reported that bioavailability of atazanavir gets enhanced when administered with food and reduces pharmacokinetic variability. Oral bioavailability is found to be 60-68%. [12-17].

MATERIALS AND METHOD

Atazanavir is obtained as gift sample from Aurobindo laboratories, hyd. Cross povidone, Cross carmellose sodium, Sodium starch glycolate are the superdisintegrants obtained from AVEB chemicals. Aerosil, Sweetener, Banana flavour, Talc, Magnesium stearate used are of analytical grade.

Direct compression method

Drug, polymer and diluent were weighed accurately according to the formula and mixed in geometric proportions using a mortar and pestle. The mixture was passed through sieve no 30 and thoroughly mixed in a polythene bag for 15 mins. The powder blend was then lubricated with Aerosil, talc and magnesium stearate for 5 mins. Polymer used were cross povidone (CP), cross carmellose sodium (CCS), sodium starch glycolate (SSG) at different polymer concentrations like 5%,7.5%,10%,12.5%,15%. The Drug -Polymer

ratio was developed to adjust drug release as per theoretical release profile.

Finally the powdered blend was compressed into tablets on a 16 station rotary punching machine with 8 mm round, flat faced punches. All the formulations were prepared by direct compression method.

Table 1: Formulation development of atazanavir oral disintegrating tablets

Ingredients	Formulation codes														
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Atazanavir	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
CP	5	7.5	10	12.5	15										
CCS						5	7.5	10	12.5	15					
SSG											5	7.5	10	12.5	15
Lactose	74	71.5		66.5	64	74	71.5	70	66.5	64	74	71.5	70	66.5	64
Aerosil	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Sweetner	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Banana flavour	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total (mg)	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

PRECOMPRESSION PARAMETERS

The flow properties of the prepared powdered blend was evaluated for parameters like Angle of repose [18], Bulk density, Tapped Density [19], Compressibility index and hausner ratio [18].

EVALUATION OF TABLETS

Weight variation [20] of the tablets was determined by using shimadzu weighing balance. Crushing strength [21] of the tablets was measured by using Monsanto hardness tester. Thickness [21] of the tablets was determined by using digital vernier calipers.% Friability [21] of the tablets was measured by using Roche friabiliator which is rotated for 100 revolutions.

Wetting Time [22]

Five circular tissue papers of 10 cm diameter are placed in a Petridish. 10 mL of water-containing amaranth a water soluble dye is added to petridish. Compressed tablets were carefully placed on the surface of the tissue paper. The time required for water to reach to the upper surface of tablet was noted as a wetting time. The procedure was repeated on 6 tablets and mean values was recorded.

In-vitro Disintegration Test [22]

The test was performed on 6 tablets using Tablet disintegration tester Labindia, Mumbai, India). 0.01N Hcl was used as a disintegration media. The time taken by the tablets to disintegrate completely was measured in seconds.

Drug content uniformity [20]

Six tablets were powdered using mortar and pestle and equivalent weight of 200 mg of Atazanavir was transferred into a 100 ml volumetric flask and dissolved using 0.01N Hcl. The solution was filtered and diluted suitably. Drug content was measured at 246 nm using UV-spectrophotometer (Shimadzu 1700, Japan).

In-vitro drug release studies [20]

The in-vitro drug release studies of Atazanavir from oro disintegrating tablets were carried out using USP dissolution test apparatus type-II (Paddle type) rotated at 50 rpm in 900 ml of dissolution medium (0.01N HCl) and temperature maintained at 37±0.5°C. At specified time intervals, 5 ml samples were collected and immediately replaced with an equal volume of fresh prewarmed medium. Samples were suitably diluted and analyzed by using UVspectrophotometer (Shimadzu 1700, Japan) at 246 nm. All the tests were carried out in triplicate.

CHARECTERIZATION DRUG AND EXCIPIENT COMPATIBILITY

Differential scanning calorimetric studies (DSC) [23]

Thermal properties of pure drug atazanavir and the formulations were evaluated by Differential Scanning Colorimetry (DSC) using DSC 200 F3 instrument. The samples were placed in standard aluminium pans and sealed with a lid. Heating scans by 10k/min were applied with a nitrogen purge of 60ml/min over a temperature range of 00 to 450 ^{o}C. An aluminium pan was used as a reference. A quality equivalent to 2 mg of pure drug was used for the study.

Fourier transform infrared spectroscopy (FT-IR) [24]

The drug - excipients interaction were studied using Fourier transform infrared spectrophotometer (FTIR). IR spectra for drug and powdered tablets were recorded in a Fourier transform infrared spectrophotometer (FTIR 1615, Perkin Elmer,USA) with Potassium Bromide (KBr) pellets.

RESULTS AND DISCUSSION

Precompression parameters

The prepared powder blend of the formulations was evaluated for flow properties as per the reported procedure. The angle of repose of the entire blend in all the formulations were found to be in the range 26^{0} 86"±1.05 to 31^{0} 29" ±1.01. The Bulk Density was found to be in the range of 0.379±0.12 to 0.461±0.08 and Tapped Density ranged from 0.452±0.09 to 0. 0.511±0.03 respectively. Percent Compressibility index was found between 21.53±1.07 to 26±1.08. The Hauser ratio ranged from 1.24±0.09 to 1.38±0.05.

Post compression parameters

The compressed tablets of different formulations were evaluated for various compression parameters like weight variation, hardness, thickness, friability, Wetting time, Disintegration time and % drug content. All the formulated tablets of the formulations passed weight variation test within the pharmacopoeia limits. The weight of all the tablets was found to be uniform. Tablets mean thickness were uniform in all the formulations and were found to be in the range of 3.19 to 3.57 mm. The measured hardness of tablets of each batch ranged between 2.4 to 3.43 kg/cm2. The value of % Friability of each batch was found to be in the range of 0.51 % to 0.72% which ensures that the tablets can withstand to the mechanical shocks during transportation and handling. All formulations showed less than 1% (w\w) friability. % the wetting time of the formulation was found to be between 7.2 mins to 45 secs. The invitro disintegrating time was in the range of 4.1 mins to 21 secs. Wetting time and invitro disintegrating time was found to get decreased as the concentration of superdisintegrants was increased. Drug content of all the formulations were uniform and were found to be in the range of 97% to 99.6%. All the tablets conformed to the requirement of assay, as per I.P.

% Invitro release of atazanavir from oral disintegrating tablets

The release rate of Atazanavir from oral disintegrating tablets was determined using USP dissolution testing apparatus II (paddle type) at 50 rpm using 0.01 N HCl as dissolution medium. Atazanavir oral disintegrating tablets were prepared by using super disintegrant like

cross povidone, cross carmellose sodium, sodium starch glycolate. Drug release of Atazanavir from all the formulations F1 to F5 ranged from 50.3 to 74.6% during the first 5 mins, it was between 80 and 99 % by 30 mins. . Drug release of Atazanavir from all the formulations F6 to F10 ranged from 54.5 to 76.5% during the first 5 mins, formulation F10 showed complete drug release within 15 mins. Drug release of Atazanavir from all the formulations F11 to F15 ranged from 61.8 to 85.5% during the first 5 mins, formulation F15 showed complete drug release within 20 mins. The release of Atazanavir mainly depends upon the super disintegrant concentration. It was found that, increase in the content of superdisintegrants, increased the drug release.

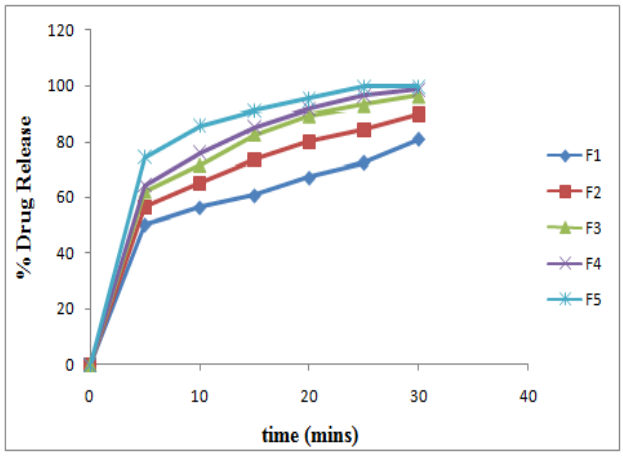

Fig 1: Cumulative % drug release Atazanavir oral disintegrating tablets prepared with cross povidone.

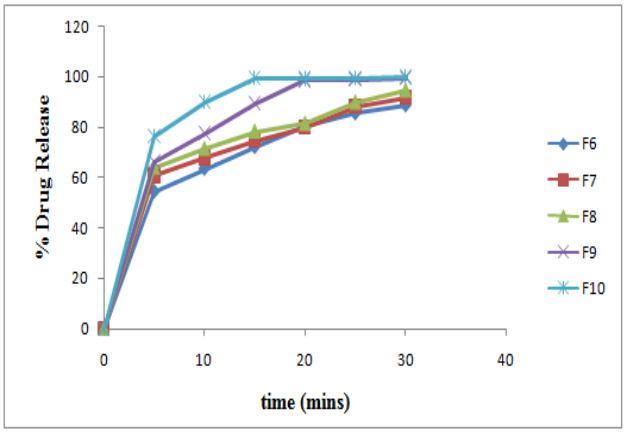

Fig 2: Cumulative % drug release Atazanavir oral disintegrating tablets prepared with crosscarmellose

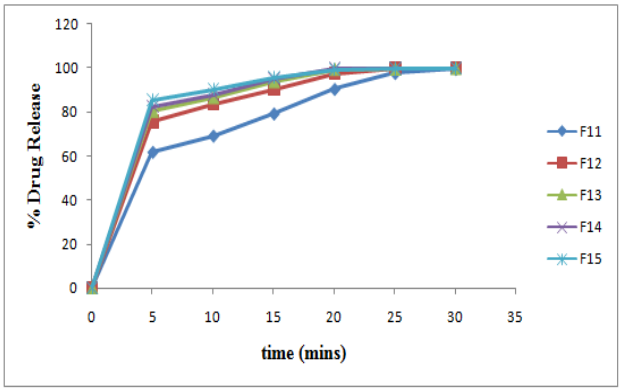

Fig 3: Cumulative % drug release Atazanavir oral disintegrating tablets prepared with Sodium starch Glycolate

Differential scanning calorimetry (DSC) Study

DSC study was conducted on the pure drug and OD tablets. DSC thermogram of pure Atazanavir showed sharp endothermic peak at 208.2 ^{0}C. Similar endothermic peak was obtained with the formulations containing Atazanavir and crosspovidone at 207.1 ^{0}C, Atazanavir with Cross carmellose sodium at 206.5 ^{0}C and Atazanavir with SSG at 207.8 ^{0}C. This clearly indicates that there is no interaction between the pure drug and superdisintegrants.

Fourier transforms infrared Radiation measurement (FT-IR)

FTIR study was performed on the selected formulation prepared with different superdisintegrants such as pure Atazanavir and with CP, CCS and SSG. The spectrum peak points of the formulation were similar with that of the pure Atazanavir, clearly indicating that there is no interaction within pure drug and superdisintegrants.

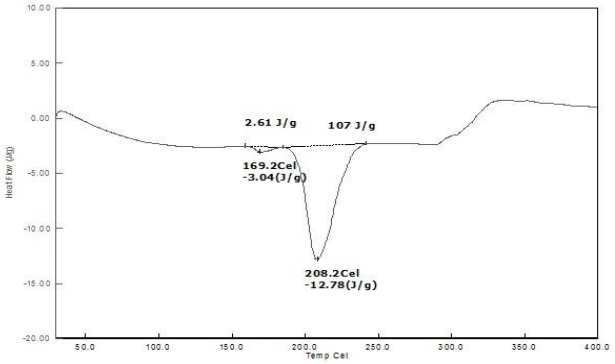

Fig 4: DSC thermogram of pure Atazanavir

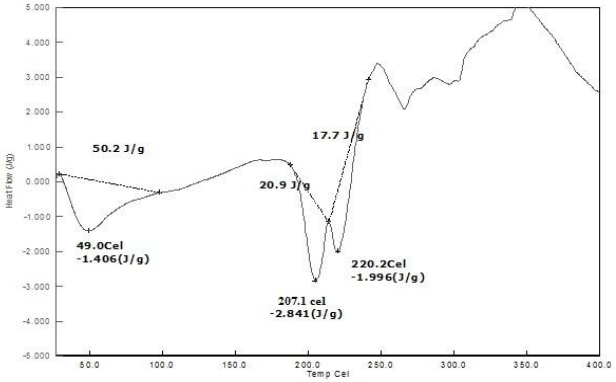

Fig 5: DSC thermogram of Atazanavir oral disintegrating tablets prepared with Crosspovidone

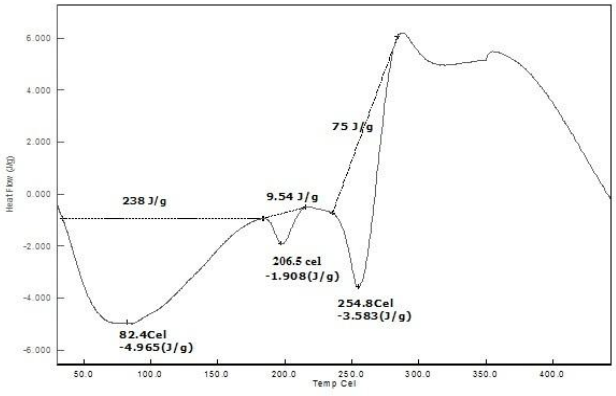

Fig 6: DSC thermogram of Atazanavir oral disintegrating tablets prepared with Cross carmellose.

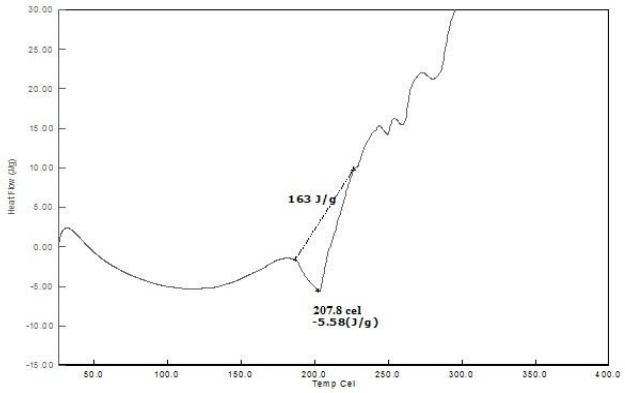

Fig 7: DSC thermogram of Atazanavir oral disintegrating tablets prepared with Sodium starch glycolate

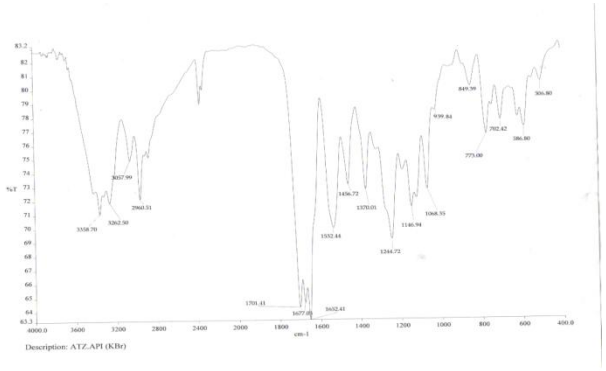

Fig 8: FTIR spectrum of Pure Atazanavir

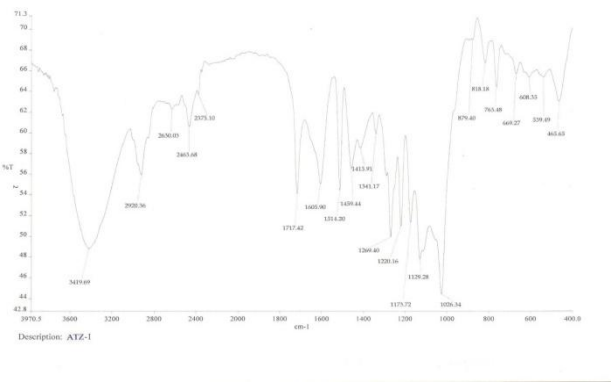

Fig 9: FTIR spectrum of Atazanavir oral disintegrating tablets prepared with Crosspovidone

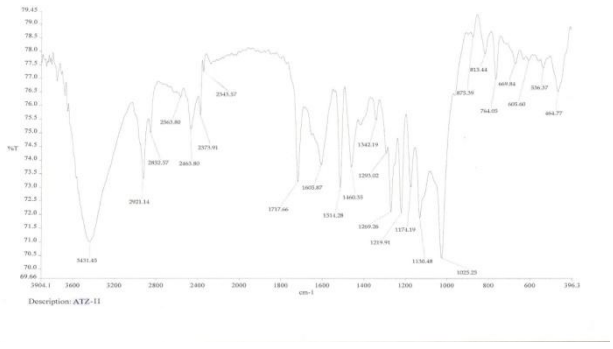

Fig 10: FTIR spectrum of Atazanavir oral disintegrating tablets prepared with Cross carmellose sodium

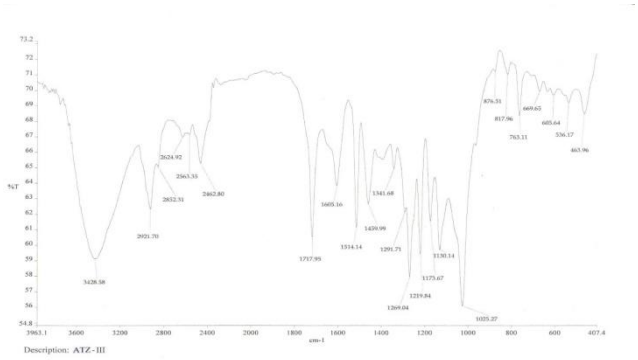

Fig11: FTIR spectrum of Atazanavir oral disintegrating tablets prepared with Sodium starch Glycolate

CONCLUSION

The present investigation of this study was undertaken with an aim to formulate and characterize oral disintegrating tablets of Atazanavir using direct compression method with super-disintegrating agents. The results of micromeritic evaluation confirmed that the powder blend has good flow properties. Quality control test results were within the pharmacopoeial limits. It was concluded that the formulation F10 containing 15% crosspovidone was found to be promising showing disintegration time of 21 seconds, wetting time of 45 second and highest dissolution rate of 99.3% in 15 min when compared to other formulations. FTIR and DSC study confirmed that there is no drug-excipients interaction between Atazanavir and excipients.

REFERENCES

1. Sastry SV, Nyshdham JR, Fix JA Recent technological advances in oral drug delivery: A review. Pharmaceutical Science and Technology Today 2000; 3:138-45.
2. Seager H Drug-delivery products and the Zydis fast-dissolving dosage form. Journal of Pharmacy and Pharmacology 1998; 50(4):375-82.
3. Lindgren S, Janzon L Dysphagia; Prevalence of swallowing complaints and clinical findings. Medical clinics of North America 1993; 77:3-5.
4. Kundu S, Sahu PK Recent trends in development of ODT: A review. Trop Journal Pharm Res 2009; 8(2):161-172.
5. Jha SK, Geethalakshmi A, Bhatia V, Shukla TP ODT: A technology for mankind. Journal of Global Pharma Technol 2010; 2:11-17.
6. Mehta K et al., An emerging trend in oral drug delivery technology: Rapid disintegrating tablet. J Pharm Sci Technol 2010; 2:318-329.
7. Fu Y, Yang S, Jeong SH, Kimura S, Park K Orally fast disintegrating tablets: Developments, technologies, taste-masking and clinical studies. Critical Review in Therapeutic Drug Carrier System 2004; 21:433-76
8. Brown D. Orally Disintegrating Tablets- Taste over Speed. Drug Delivery Technology 2003; 3:58-61.
9. Habib W, Khankari R, Hontz J Fast-dissolving drug delivery systems, critical review in therapeutics. Drug Carrier Systems 2000; 17(1):61-72.
10. Chang R, Guo X, Burnside BA, Couch R Fast-dissolving tablets. Pharm. Tech 2000; 24(6):52-58.
11. Kuchekar BS, Badhan AC, Mahajan HS Mouth dissolving tablet: A novel drug delivery system. Pharma Times 2003; 35:7-9.
12. Croom KF, Dhillon S, Keam SJ Atazanavir: a review of its use in the management of HIV-1 infection. Drugs 2009; may 29; 69(8):1107-40. doi: 10.2165/00003495-200969080-00009. Pub med
13. von Hentig N Atazanavir/ritonavir: a review of its use in HIV therapy. Drugs Today (Barc) 2008; Feb, 44(2):103-32. Pub med

14. Swainston Harrison T, Scott LJ Atazanavir: a review of its use in the management of HIV infection. Drugs 2005; 65(16):2309-36. Pub med
15. Le Tiec C, Barrail A, Goujard C, Taburet AM Clinical pharmacokinetics and summary of efficacy and tolerability of atazanavir. Clin Pharmacokinetics 2005; 44(10):1035-50. Pub med
16. Lopez-Cortes LF [Pharmacology, pharmacokinetic features and interactions of atazanavir] Enferm Infecc Microbiol Clin 2008; (Dec; 26 Suppl 17):2-8. Pub med
17. Busti AJ, Hall RG, Margolis DM Atazanavir for the treatment of human immunodeficiency virus infection. Pharmacotherapy 2004; Dec, 24(12):1732-47. Pub med
18. United States of Pharmacopeia-National Formulary. USP 30 – NF 25. The Unit States Pharmacopeial Convention, Rockville, MD, 2007, Volume 1, 644, 242, 645, 731 and 634.
19. Shah D, Shah Y, Rampradhan M Development and evaluation of controlled release diltiazem hydrochloride microparticles using cross-linked polyvinyl alcohol. Drug Dev Ind Pharm 1977; 23:567 – 574.
20. Indian Pharmacopoeia, Ministry of Health and Family Welfare, Govt. of India. 4th Ed. New Delhi. The controller of publications; 1996. A-54.
21. Lachman L, Lieberman HA, Kinig JL The Theory and Practice of Industrial Pharmacy. Varghese Publishing House; 1991. 67-68.
22. Battue, Repay SK, Maunder S, Rio MY Formulation and evaluation of rapidly disintegrating tablet Fenoverine tablets: Effect of superdisintegrants. Drug Dev Ind Pharm 2007; 33:1225-1232.
23. Patel R, Shardul N, Patel J, Baria A Formulation Development and Evaluation of Mouth Melting Film of Ondansetron Arch Pharm Sci & Res 2009; 1(2):212-217.
24. Behin Sundara Raj, Punitha ISR, Suraj Dube Formulation and Characterization of Fast Disintegrating tablets of Amlodipine using Superdisintegrants. Journal of Applied Pharmaceutical Science 2012; 02 (08): 118-123.