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Research

Formulation and evaluation of atazanavir Sulphate Capsules Of 150mg

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Abstract

Recommendations for a highly active antiretroviral therapy (HAART) in either pretreated patients or symptomatic patients with an AIDS-defining event are based on a combination of three or more agents from different antiretroviral classes including two nucleoside reverse transcriptase inhibitors with atleast one protease inhibitor. The majority of currently available protease inhibitors are co-administered with low-dose ritonavir as a pharmaco-enhancer that significantly increases protease inhibitor plasma concentrations. Atazanavir is a highly active aza peptide inhibitor of the HIV protease. It was the first and to date the only, protease inhibitor designed to be applied once daily (q.d.) and is expected to overcome the problems of earlier agents of this class of drugs, such as unfavourable adverse events like hyperlipidemia, diarrhea and lipodystrophy. Atazanavir, formerly known as BMS-232632, can be dosed either at 400 mg q.d. without a pharmaco-enhancer as first-line HIV therapy or combined with ritonavir as atazanavir/ritonavir 300/100 mg q.d. for therapy-experienced patients. However, atazanavir it self also enhances plasma concentrations of other co-administered HIV-1 protease inhibitors, so that its use as a combination partner in boosted double protease inhibitor combinations, with or without the addition of nucleoside reverse transcriptase inhibitors, is being evaluated. Unboosted atazanavir is approved for first-line HIV therapy in adults in the United States, and atazanavir/ritonavir is recommended for the second-line therapy of HIV-1 infection in adult HIV-1-infected patients in the United States and the European Union. More recently, data from the CASTLE study (AI424-138) have been reported at the 15th Conference on Retroviruses and Opportunistic Infections by Molina et al., where boosted atazanavir-containing HAART was compared to a regimen with lopinavir/ritonavir in therapy-naive patients.

Keywords: Formulation, Evaluation, Atazanavir sulphate, HIV

INTRODUCTION

Atazanavir Sulphate (ATV) is widely used as anti-HIV agent having poor aqueous solubility needs to modulate novel drug delivery system to enhance therapeutic efficiency and safety. The main objective of the present work was to fabricate ATV-loaded nano structured lipid carriers (NLCs) employing quality by design (QbD) approach to address the challenges of bioavailability and their safety after oral administration.

Herein, the main objective was to identify the influencing variables for the production of quality products.

Considering this objective, quality target product profile (QTPP) was assigned and a systematic risk assessment study was performed to identify the critical material attributes (CMAs) and critical process parameter (CPP) having an influence on critical qualityattributes (CQAs). Lipidconcentrations, surfactant concentrations, and pressure of high-pressure homogenizer were identified as CMAsW`3QFixed-dose combination drugs can be defined as two or more drugs in a single formulation, each drug having independent mode so faction, or the combination of which are synergistic or additive, or complementary in their effect. "Free" combinations can be defined as two or more drugs in separate formulations, each taken usually at the same time.

Fixed-dose combination (FDC) products are common in the treatment of hypertension, diabetes, human immune deficiency virus, and tuberculosis. They make it possible to combine two or more drug molecules with different modes of pharmacological actions in a single dosing unit and optimize the treatment. From a patient perspective, they offer convenience, reduced dosing unit burden, and cost savings.

MATERIALS AND METHODS

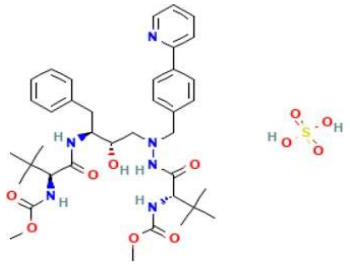
Api-atazanavir sulphate capsule, binder- povidone (pvpk30), filler- microcrystalline cellulose (mcc), disintegrant-croscamellose sodium, lubricant- magnesium stearate wetting agent-Water gelatin protein derived from animal collagen titanium dioxide water, To dissolve the gelatin plasticizer glycerin colorants titanium dioxide (white) Opacifiers bovine or povine.

Equipments

Capsule filling machine, high, shear, mixer, or granulator, fluidized bed dryer, sieve or screen Blender (v-cone,blender)-weighing, balance.

Drug profile

Drug: Atazanavir Sulphate
Drugcategory: protease inhibitor (pI) class**.**
MolecularFormula:C38H52N607
MolecularWeight:802.93g/mol.



Pre-formulationstudies

Solubility Profile

Aqueous Solubility: Atazanavir Sulphate is practically insoluble in water at neutral pH (about 7) but exhibits pH-dependent solubility. Its solubility increases in acidic conditions (e.g.,pH1.2), making it more soluble in the stomach's acidic environment.

Organic Solubility: It is more soluble in organic solvents like methanol, ethanol, and DMSO.

Biopharmaceutical Classification System (BCS)

Atazanavir is a BCS Class II drug, which means it has low solubility but high permeability. This property impacts its formulation and necessitates strategies to enhance its dissolution for improved bioavailability.

Particle Size and Shape

Particle Size: Optimal particle size is typically below 20microns for improved dissolution and bioavailability in oral formulations. Reducing particle size through micronization can help increase the drug's surface area, leading to enhanced dissolution.

Particle Shape: Atazanavir Sulphate crystals generally have a needle-like or elongated shape. However, specific particle shapes may vary depending on the manufacturing process. Shape can affect the flow properties and compressibility, which are important for capsule filling and uniform dosing.

pKa (Acid Dissociation Constant)

pKa Values: Atazanavir Sulphate has multiple pK a values due to its complex molecular structure:
The pKa1 is around 4.1, associated with the basic functional group.

The pKa2 is approximately 9.2, related to its secondary amine group.
These pKa values indicate that Atazanavir can exist in different ionic forms depending on the pH, which influences its solubility and absorption in various segments of the gastrointestinal tract.

Polymorphism
Polymorphic Forms: Atazanavir Sulphate can exist in different crystalline forms, but the most commonly used form in pharmaceutical formulations is the anhydrous crystalline form. Polymorphic forms can exhibit differences in solubility, stability, and bioavailability.
Impact on Formulation: Polymorphic stability is critical, as changes in form can lead to variability in dissolution rates and therapeutic efficacy. During formulation, it is essential to maintain the polymorphic form to ensure consistency in drug performance.

Partition Coefficient (LogP)
Log P: Atazanavir has a Log P value of approximately 4.3. This value indicates that it is lipophilic and has high permeability across biological membranes.

Implications for Absorption
Its lipophilic nature allows Atazanavir to readily cross cell membranes, which aids in absorption in the gastrointestinal tract. However, its low solubility poses challenges, often addressed by using solubility-enhancing techniques in the formulation.

Evaluations tests
Stabilitytests
Shell Integrity Test
Purpose: To ensure that the capsule shell is intact and provides adequate protection for the contents.
Method: Visual inspection under adequate lighting to check for cracks, splits, dents, or deformation in the capsule shells.
Acceptance Criteria: Capsules should be free from any visible defects. They should not exhibitsigns of physical damage or leakage. This test may also included tactile assessment to ensure that the capsules are not too brittle.

Determination of Shelf Life
Purpose: To establish the period during which the capsules retain acceptable quality under specified storage conditions.
Method: Conduct stability testing under both accelerated (e.g., 40°C and 75% RH for 6 months) and long-term conditions (e.g., 25°C and 60% RH for up to 24 months), following International Council for Harmonization (ICH) guidelines.
Parameters Monitored: During testing, evaluate appearance, weight variation, assay (active content), disintegration, dissolution, and other critical quality attributes.
Acceptance Criteria: Capsules should meet specification requirements for all tested parameters at the end of their determined shelf life. Based on the stability results, assign a shelf life, typically 24 months for long-term stability.

Invariabilitytests
Weight Variation Test
Purpose: To ensure uniformity of weight, which indirectly verifies consistent filling?
Method: Weigh 20 individual capsules. Calculate the average weight and determine the deviation of each capsule from this average.
Acceptance Criteria (per USP): For capsules containing 150 mg of active ingredient (more than 25mg or 25% of the total weight), the weight of each capsule should bewithin±7.5%of the average weight.

Content Uniformity Test
Purpose: To ensure each capsule contains the appropriate dose of Atazanavir Sulphate.
Method: Perform an assay on the content of the active ingredient in 10 individual capsules using HPLC (high-performance liquid chromatography) or UV spectrophotometry.
Acceptance Criteria: The content of Atazanavir Sulphate in each capsule should be within 85% to 115% of the label claim. No more than one capsule can be outside this range, and none should fall outside 75% -125%.
Disintegration Test
Purpose: To confirm that the capsules disintegrate within a specified time, facilitating drug release.
Method: Place one capsule in each tube of the disintegration apparatus, using simulated gastric fluid (0.1 NHCl) at 37°C. Run the apparatus until all capsules have fully disintegrated.

Acceptance Criteria (per USP for immediate-release capsules): Capsules should disintegrate within 15 minutes in simulated gastric fluid.

Dissolution Test
Purpose: To ensure that the drug releases at an appropriate rate for absorption.
Method: Use a dissolution apparatus (USP Apparatus I or II) with 900 mL of 0.1 N HCl at 37°C as the dissolution medium. The apparatus should run at an appropriate rotation speed (e.g.50-75 rpm for Apparatus II).
Sampling: Withdraw samples at specific time points (e.g., 5, 10, 15, 30, and 45 minutes) and analyze using HPLC or UV spectrophotometry.
Acceptance Criteria: Generally, at least 80% of the drug should dissolve within 30 minutes for immediate-release capsules, though specific criteria should align with product specifications.

Moisture Permeation Test
Purpose: To assess the capsule shell's resistance to moisture, especially important for hygroscopic drugs like Atazanavir Sulphate.
Method: Place a desiccant inside capsules and subject them to specific humidity conditions (e.g., 75% RH at 25°C) for a set duration. Then, weigh the capsules to determine moisture uptake.
Acceptance Criteria: The moisture gain should be within a specified limit (usually below 5% for sensitive drugs) to ensure that the drug remains stable during storage.

Stability Studies
Capsules are subjected to stability testing under different conditions, including accelerated (e.g.,40°C/75%RH) and long-term (e.g.,25°C/60%RH) conditions. Samples are analyzed at various time points to assess changes in physical appearance, assay, dissolution, and degradation products.
Purpose: Evaluates the shelf life and ensures the drug maintains its efficacy and safety over time.

Microbial Testing
Conduct microbial tests to ensure the capsules are free from harmful bacteria, fungi, and other microorganisms. This typically involves total viable aerobic count (TAMC), total yeast and mold count (TYMC), and testing for specific pathogens like E. coli and S. aureus.
Purpose: Ensures the product is safe from microbial contamination.

Capsule Hardness (if applicable)
Measure the force required to break or crush the capsule using a hardness tester. This is more commonly done for tablets, but can be relevant for capsules if they are prone to damage.
Purpose: Ensures the capsules are robust enough how it stand handling but will still disintegrate properly.

Identification Tests
Various tests (e.g., infrared spectroscopy, HPLC, or UV-spectrophotometry) are used to confirm the identity of Atazanavir Sulphate in the capsules.

Purpose: Ensures that the correct active ingredient is present in the formulation.

Different quantity of ingredient were change for the formulation to optimized the formula

Ingredient	Quantityinbatchperkg(mg/Tablets)						
	Trail 1	**Trail 2**	**Trail 3**	**Trail 4**	**Trail 5**	**Trail 6**	**Trail 7**
Atazanavir Sulphates USP	341.71	341.71	341.71	341.71	341.71	341.71	341.71
Lactose Monohydrates USP	160	161	161.5	162	162.8	162.89	162.89
povidone	22.89	21.89	21.39	20.89	20.09	20.00	20.00
Purified water	450.00	450.00	450.00	450.00	450.00	450.00	450.00
Lubrication							
povidone	9.00	9.20	09.30	10.40	9.10	10.00	10.00
Magnesium stearate	6.40	5.20	5.10	5.00	5.30	5.40	5.40

							540.0
Flow Properties	Very Poor	Poor	Passable	Fair	Good	Excellent	Excellent

Granulation control	**Trail 1**	**Trail 2**	**Trail 3**	**Trail 4**	**Trail 5**	**Trail 6**	**Trail 7**
Total Drying time	5 min	5 min	5 min	5 min	5 min	5 min	5 min
Inlet Granulation Stage Temperature of FBD	57-68	61-69	55-62	54-64	55-64	53-61	52-62
Out let Temperature of FBD	20-32	29-35	29-39	30-55	39-50	27-35	28-38
Impeller Speed (RPM50)	20	20	20	20	20	20	20
Amperage Impeller	10	11	10	10	10	11	10
Chopper off	Off	Off	Off	Off	Off	Off	Off
Amperage Impeller	10	12	11	11	10	10	12
Chopper ON slow RPM1500	3	3	3	3	3	3	0
Blender RPM	15	15	15	15	15	15	15
Blending time	5	5	5	5	5	5	5
LossofDrying	2.0	1.3	0.6	1.4	0.6	1.4	1.4
Bulk density (g/ml)	0.352	0.432	0.622	0.523	0.588	0.455	0.456
Tappeddensity (g/ml)	0.243	0.312	0.494	0.434	0.404	0.695	0.693
Angle of Repose	30	46	42	39	35	29	29

Granulation control	**Trail 1**	**Trail 2**	**Trail 3**	**Trail 4**	**Trail 5**	**Trail 6**	**Trail 7**
CarrsIndex	33	28	22	17	13	<10	<10
HausnerRatio	1.47	1.37	1.28	1.22	1.3	0.9	0.9
Flow Properties	Very Poor	Poor	Passable	Fair	Good	Excellent	Excellent
Compressibility index(%)	31.803	37.997	29.594	67.696	37.994	38.805	38.801
WaterContent byKF	2.25	4285	2.15	2.50	2.05	2.15	2.16

From the above table all in processcontrol and parameter is observed well within criteria for Trail batches Trail 6 and Trail 7.

Blend Uniformity	**Criteria**	**Trail 1**	**Trail2**	**Trail3**	**Trail4**	**Trail5**	**Trail6**	**Trail7**
				Granulation Stage:				
Description	light yellow powder	light yellow powder	light yellow powder	light yellow powder	light yellow powder	light yellow powder	light yellow powder	light yellow powder
Assayby HPLC	95-1025 % labelled claim	98.3	99.1	98.2	100.3	96.4	100.5	100.2
				Particle size analysis: For information				
#30	1849	21.49	25.49	26.89	25.39	26.49	27.49	23.92
#40	34.00	22600	27.00	34.00	36.00	34.00	36.00	32.83
#60	39.54	28.83	38.59	36.55	38.53	36.53	37.59	34.83
#80	48.09	26.83	42.09	47.09	46.03	42.09	3.809	35.92
#100	47.05	38.92	45.00	45.03	44.02	44.00	45.05	46.21

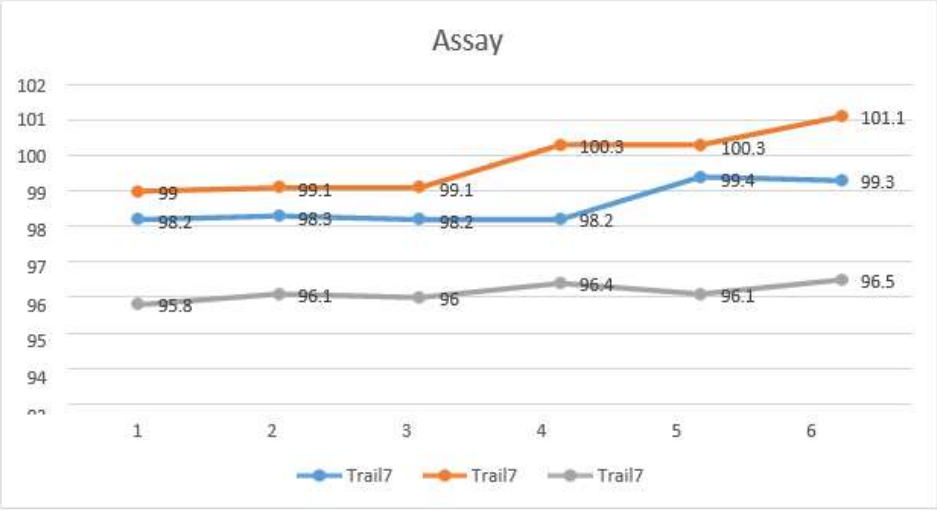
Weight variation of 10 filled capsule

Trail	Criteria	Weightvariationof10filled capsule
Trail1	3.460.0mg	3.42
Trail2	3.356-3.564.	3.02
Trail3		3.29
Trail4		3.84
Trail5		3.08
Trail6		3.36
Trail7		3.32

Trail	Criteria	Weightvariationof10filledcapsule
Trail1	NMT30min	19min,42sec
Trail2		19min,05sec
Trail3		19min,28sec
Trail4		19min,10sec
Trail5		19min,07sec
Trail6		19min,19sec
Trail7		19min,12sec

Assay of Capsule

Assay	Trail7	Trail7	Trail7
1	98.2	99.0	95.8
2	98.3	99.1	96.1
3	98.2	99.1	96.0
4	98.2	100.3	96.4
5	99.4	100.3	96.1
6	99.3	101.1	96.5
Mean	99.1	100	96.2
SD	1.24	1.13	0.26
%RSD	1.25	1.13	0.27
HPLC	QC- HPLC001	QC- HPLC001	QC- HPLC001
Column	QC-COL- 011	QC-COL- 011	QC-COL- 011



Dissolution Profile: InpH 6.8Phosphatebuffer and2%SLSat75 RPMUSP 1

	Time	Specification	Trail7	Trail7	Trail7
1	10nd min	NMT 30%	23	22	28
2			23	21	29
3			25	25	27
4			26	24	26
5			28	22	25
6			29	24	22
1	20th min	Between60-80%	72	75	79
2			78	76	73
3			79	76	75
4			75	78	76
5			76	69	79
6			79	79	75
1	45th min	NLT80 %	99.8	99.3	100.5
2			98.9	98.2	100.5
3			98.7	98.6	100.4
4			98.3	98.4	99.5
5			99.4	99.7	101.6
6			99.3	99.8	99.6

SUMMARY

Atazanavir sulfate capsules are an important antiretroviral medication used to manage HIV infection. As part of the protease inhibitor class, Atazanavir works by blocking the HIV protease enzyme, which is necessary for the virus to mature and replicate. By inhibiting this enzyme, Atazanavir helps to reduce the viral load in the body, slowing down disease progression and supporting the immune system's function.

Typically prescribed at 150mg and often boosted with ritonavir to enhance its effectiveness, Atazanavir is usually taken once daily with food, which improves its absorption and reduces, The chance of side effects. Common side effects may include gastro intestinal discomfort, such as nausea, vomiting, and diarrhea, as well as jaundice due to increased bilirubin levels. While rare, more serious side effects can include abnormal heart rhythms, kidney stones, and liver toxicity. Consequently, regular monitoring of liver and kidney function is necessary during treatment. With food, and are often combined with other medications, like ritonavir, to boost their effectiveness. These prepared capsules aim to provide reliable dosing, reduce common side effects (like gastrointestinal discomfort and jaundice), and facilitate easier handling for healthcare providers and patients. They may also be formulated to minimize drug inter actions and Improve stability, ensuring that the medication remains effective over its shelf life. Overall, prepared at azanavirsulfate capsules playakeyrolein HIV treatment by ensuring consistent, high-quality dosing that supports better patient adherence and treatment outcomes.

CONCLUSION

Atazanavir sulfate150mg capsules are an effective antiretroviral treatment form an aging HIV infection by inhibiting viral replication. When taken as directed, often with other medications and alongside food, Atazanavir can significantly reduce viral load, helping patients maintain immune function. However, its use requires careful monitoring for potential side effects like jaundice, and attention to drug interactions. Overall, atazanavir is a valuable component of HIV therapy, though it requires individualized care and strict adherence for an optimal results. In conclusion, the project achieved its primary objectives by effectively addressing the outlined goals and delivering impactful results. Through a combination of strategic planning, diligent execution, and collaboration, the project successfully met key performance indicators, staying within scope, timeline, and budget. The project outcomes

Demonstrate significant progress in the targeted areas, laying a strong foundation for future work and offering valuable insights for continuous improvement. Overall, this project not only fulfilled it so objectives but also contributed meaningfully to the organization’s broader mission and goals. The formulation the drug release up to 45 minutes.. The formulation prepared with lactose monohydrates Crospovidone and magnesium stearates Dry and wet granulation procedure was the chosen technology for the preparation of Atazanavir Sulfate capsule. Based on the preliminary studies, different formulation trials (F1-F7) were carried out with different concentration so f Disintegrants, diluents. From the various formulations it was decided that the formulation batch of F7 was finalized as the optimized formula. Formulation F7 showed satisfactory results with various physicochemical evaluation parameters like Disintegration time, Dissolution profile, Assay when matched with that of the marketed

product. The stability studies at all condition indicates that the formulated capsules were found to be stable. Hence, it is finally concluded that, Atazanavir Sulfate capsules are pharmaceutically comparable, low cost, quality improved and stable formulation. This study has potential commercial and industrial applications after establishing the real-time stability, safety and efficacy.

REFERENCES

1. Sathali AH, Gopinath G. Formulation and evaluation of paliperidone nanocrystals. J. Biomed. Med. 2013;1(5):422-38.
2. Hecq J, Deleers M, Fanara D, Vranckx H, Amighi K. Preparation and characterization of nanocrystals for solubility and dissolution rate enhancement of nifedipine. Int J Pharm. 2005 Aug 11;299(1-2):167-77. doi: 10.1016/j.ijpharm.2005.05.014, PMID 15996838.
3. NagarajuK. An over view enhancement of solubility and dissolution rate. Int Res J Pharm Appl Sci. 2012 Oct 29;2(5):198-210.
4. Jain S, Patel N, Lin S. Solubility and dissolution enhancement strategies: current understanding and recent trends. Drug Dev Ind Pharm. 2015 Jun3;41 (6):875-87. doi: 10.3109/03639045.2014.971027, PMID 25342479.
5. 4.Bajaj A, Rao MR, Pardeshi A, Sali D. Nano crystallization by evaporative antisolvent technique for solubility and bioavailability enhancement of telmisartan. AAPS Pharm SciT ech.2012Dec;13(4):1331-40. doi:10.1208/ s12249-012-9860-x, PMID 23054986.
6. 5.Nagarwal C R, Kumar R, Dhanawat M, Das N, K Pandit J. Nanocrystal technology in the delivery of poorly soluble drugs: an overview. Current drug delivery. 2011 Jul 1;8(4):398-406.
7. Kumar R, Siril PF. Drop-by-drop solvent hot antisolvent interaction method for engineering nanocrystallization of sulfamethoxazole to enhanced water solubility and bioavailability. J Drug Deliv Sci Technol. 2020 Feb 1;55. doi:10.1016/j.jddst.2019.101359, PMID 101359. American-Eura J Sci Research 2010; 5 (4): 264-269
8. KumarA, Nano Cocrystals NA. Crystal engineering from a nano technological perspective. Curr Pharm Des. 2021.
9. Bhirud CH, Hiremath SN. Stability indicating RP-HPLC method for the determination of at azanavir sulphate in bulk and dosage form. Drug Invent Today. 2013 Jun 1;5 (2):81-6. Doi: 10.1016/j.dit.2013.05.008.
10. Kis O, Walmsley SL, Bendayan R. In vitro and in situ evaluation of pH- dependence of atazanavir intestinal permeability and interactions with acid- reducing agents. PharmRes.2014Sep;31(9):2404-19.doi:10.1007/s11095-014- 1336-0, PMID 24595498.
11. Xia X, Zhou C, Ballell L, Garcia-Bennett AE. In vivo enhancement in bioavailabilityofatazanavirinthepresenceofproton-pumpinhibitorsusing mesoporous materials. Chem Med Chem .2012Jan2;7(1):43-8. doi:10.1002/ cmdc.201100500, PMID 22144293.
12. Berlin M, Ruff A, KesisoglouF, Xu W,WangMH, Dressman JB. Advances and challenges in PBPK modeling--Analysis of factors contributing to the oral absorption of atazanavir, a poorly soluble weak base. Eur J Pharm Biopharm. 2015 Jun 1;93: 267-80. doi: 10.1016/j.ejpb.2015.03.031, PMID 25872159.
13. Malviya V, Ladhake V, Gajbiye K, Satao J, Tawar M. Design and characterization of phasetransition system of zolmitriptan hydrochloride fornasal drug delivery system. Int J Pharm Sci Nanotechnol. 2020 May 31;13(3):4942-51. doi: 10.37285/ijpsn.2020.13.3.8.
14. Indrayanto G, Mugihardjo HR, Handayani R. Compatibility study between famotidine and some excipients using differential scanning calorimetry. Drug Dev Ind Pharm. 1994Jan1; 20(5): 911-20. doi:10.3109/03639049409038340.
15. MalviyaVR, PandeSD, BobadeNN. Preparation and evaluation of sustained release beads of zolmitriptan hydrochloride. Res J Pharm Technol. 2019;12(12):5972-6. doi: 10.5958/0974-360X.2019.01037.0.