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Formulation and Evaluation of Ezetimibe Immediate Release Tablets

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A B S T R A C T

Ezetimibe is an orally active anti-cholesterol agent, acts by inhibiting the absorption of cholesterol at the brush border of small intestine. The objective of the present study was to formulate and evaluate immediate release tablets of Ezetimibe. The immediate release formulations were formulated by using different diluents and disintegrants like lactose monohydrate, microcrystalline cellulose of two grades 101and 102, pregelatinized starch, croscarmellose sodium. All the formulations were developed by the wet granulation method employing povidone k30 in purified water as binding agent. All the formulations were evaluated for both official and unofficial tests the results are within the limits. All the formulations were investigated for in-vitro drug release studies in 0.45% SLS in 0.05M acetate buffer pH 4.5 of volume 500 ml in USP paddle type II apparatus for 60min. The results of dissolution studies indicated that the formulation F-7 containing croscarmellose sodium, microcrystalline cellulose (Avicel 101), and lactose monohydrate, having disintegration time 3 min 10 sec and showed maximum of 96.5% of drug release with in 60min, so it is considered as optimized formulation.

Keywords: Immediate release tablets, Ezetimibe, Wet granulation method, Disintegrants.

A R T I C L E I N F O

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1. Introduction

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage forms [1]. Oral route is considered as

most natural, uncomplicated, convenient and safe due to ease to administration, patient acceptability and cost effective manufacturing process. Tablets are defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or molding methods. Tablets remain popular as a dosage form because of the advantages, afforded both to the manufacturer (simplicity and economy of preparation, stability and convenience in packing, shipping and dispensing). Although tablets are more frequently discoid in shape, they may also be round, oval, abnormal, cylindrical or triangular. They vary greatly in size and weight depending on the amount of drug substance present and intended method of administration [2].

Immediate release drug delivery system is a conventional type of drug delivery. It is designed to disintegrate and release their medicaments with no special rate controlling features. These are the dosage forms in which ≥85% of labelled amount dissolves with in 30min. However for immediate release tablets, tablet disintegrants play an important role in ensuring that the tablet matrix break up on contact with fluid in the stomach to allow the release of active drug which then become available in whole or in part, for absorption from GIT [3].

These preparations are primarily intended to achieve faster onset of action for drugs such as analgesics, antipyretics and coronary vasodilators. Other advantages include enhanced oral bioavailability through transmucosal delivery and pregastric absorption, convenience in drug administration to dysphasic patients, especially the elderly and bedridden and new business opportunities [4-7].

Conventional IR formulations include fast disintegrating tablets and granules that use effervescent mixtures, such as sodium carbonate (or sodium bicarbonate) and citric acid (or tartaric acid) and superdisintegrants such as sodium starch glycolate, crosscarmellose sodium, and crospovidone. Current technologies in fast-dispersing dosage forms include modified tableting systems, floss or Shear form technology which employs application of centrifugal force, controlled temperature and freeze-drying. Immediate release drug delivery is desirable for drugs having long biological half life, high bioavailability, lower clearance and lower elimination half life [8-10]. In the present research work an attempt was made to formulate Ezetimibe as an immediate release tablet using different diluents and disintegrants (like croscarmellose sodium, lactose monohydrate and microcrystalline cellulose and lactose monohydrate) in different proportions by wet granulation method. Ezetimibe is an anti hyperlipidemic agent which is used to lower the cholesterol levels. It acts selectively by inhibiting the intestinal absorption of cholesterol and related phytosterols. It is either administered alone or in combination with other HMG-CoA reductase inhibitors. When formulated alone it is used as an adjunctive therapy to diet and acts by reducing elevated total-C and LDL-C in patients with primary hypercholesterolemia [11, 13].

2. Material and methods

Materials: Ezetimibe was obtained as a gift sample from Hetero labs pvt.ltd, Hyderabad. Lactose monohydrate, microcrystalline cellulose, pregelatinised starch, dicalcium phosphate anhydrous, colloidal silicon dioxide, croscarmellose sodium, sodium lauryl sulphate, povidone k30 and magnesium stearate were purchased for from S.D. Fine Chem. Ltd, Mumbai, India.

Methods:

Compatibility studies between drug and excipients:

The physical compatibility of Ezetimibe as drug substance with various excipients was carried out with an aim to select suitable excipients for a stable and strong formulation. FTIR spectra of the drug and the drug with excipients were recorded in range of 4000-400 cm^{-1}. Compatibility studies were performed using FTIR spectrometer. The FTIR spectrum of the pure drug and physical mixture of the drug and excipients were studied.

Preparation of the immediate release tablets of Ezetimibe:

Sifting: Ezetimibe and microcrystalline cellulose were sifted through mesh #30. Croscarmellose sodium and sodium lauryl sulfate were sifted through mesh #40.

Binder solution preparation:

Weighed quantity of purified water was taken in a stainless steel container equipped with a propeller stirrer. Povidone was slowly added to the purified water while stirring. Continue the stirring until a clear solution is obtained.

Dry mixing: MCC, Croscarmellose Sodium and Sodium Lauryl Sulfate are loaded in to rapid mixer granulator and mixed for 10min.

Wet granulation:

Binder solution was added to the dry materials over a period of 1 to 3 minutes. Wet mass was kneaded for 1min with impellar and chopper at slow speed.

Drying: Dry the wet mass at temperature of 60°± 5°C in a rapid dryer to get LOD not more than 2.5%w/w at 105°C by auto mode using IR moisture analyzer.

Sifting and milling: Dried granules are sifted through the mesh#30 and mill the retentions using multi mill with 1.0 mm screen at slow speed/knives forward direction. Milled granules were sifted through mesh #30.

Extra granular material sifting: MCC (Avicel pH 102) and croscarmellose sodium (AC-di-sol) were sifted together through mesh #40. Magnesium stearate was sifted through mesh #60.

Pre lubrication: Load the granules in to double cone blender added sifted microcrystalline cellulose (Avicel pH 102) and croscarmellose Sodium (AC-di-sol) and mixed for 10min.

Lubrication: Sifted magnesium stearate was added to materials of above and mixed for 5minutes.

Compression: Then load the above material in to the hopper and set the parameters as specified and compressed.

Evaluation:

Precompression parameters:[14,15]

The prepared granules were evaluated for bulk density, tapped density, hausner's ratio, compressibility index and angle of repose to determine the flow and compressibility properties of the granules.

Post compression parameters: [14,15]

Weight variation test:

This is in process quality control test that has to be checked regularly. Any variation in the weight of tablets leads to either under medication or overdose. So, every tablet in each batch should have a unvarying weight. If needed corrections are made during the compression of tablets.

Method: Twenty tablets were randomly selected from the total weight of all tablets average weight was calculated. The individual weights were compared with the average weight. The % difference in the weight variation should be within the acceptable limits as per USP.

Hardness:

The resistance of tablet to chipping, abrasion or fracture under condition of storage, transportation and handling before usage depends upon its hardness. For each formulation, the hardness of 6 tablets was determined using the Schleuniger hardness tester. This tester operates in a horizontal position. An anvil driven by an electric motor presses the tablet at a constant load rate in contrast to a stationary anvil until the tablet breaks. A pointer moving along a scale indicator provides the breaking strength value/Hardness value.

Friability:

Friability of the tablets was determined using Roche Friabilator. This test focuses a number of tablets to the combined effect of shock and abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of preweighed 6 tablets was placed in Roche Friabilator which was then operated for 100 revolutions i.e. 4 minutes. The tablets were then reweighed. A loss of less than 1 % in weight is generally measured acceptable**.** Percent friability (% F) was calculated as follows,

%F = (Initial weight – Final weight)/ Initial weight × 100

Disintegration time

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in USP disintegration test apparatus. It consist of 6 glass tubes which are 3 inches long, open at the top, and held against a 10 mesh screen, at the bottom of the basket rack assembly. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 liter beaker containing 0.4% SLS in 0.05M acetate buffer pH 4.5 at 37°C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablet was noted.

Dissolution study:

Preparation of dissolution medium: [16,17]

Weigh and transfer 6.8g of sodium acetate trihydrate into a beaker containing 1000ml of water sonicate dissolve. Adjust P^H of the solution to 4.5± 0.5 with glacial acetic acid. To the above solution add 4.5g of sodium lauryl sulfate and sonicate to dissolve.

Test procedure: The test is carried out in USP type II (paddle) apparatus. The dissolution medium is placed in the beakers and heated so as to obtain and maintain a temperature of 37.0ºc ± 0.5ºc. The paddles are rotated at 50 RPM and the prepared tablets were placed in each basket and the samples were withdrawn at 10, 20, 30 and 45 min and the same amout of media is replaced to maintain the sink conditions during the process. The samples are spectrometrically analyzed for Ezetimibe at 232nm.

3. Results and Discussion

Drug excipient compatibility studies: The results of both physical and chemical compatibility have shown that all the selected ingredients were compatible with drug.

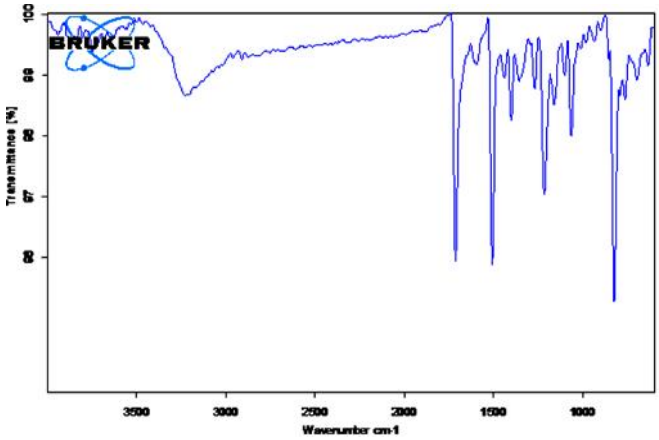

Figure 1: FT-IR spectrum of Ezetimibe

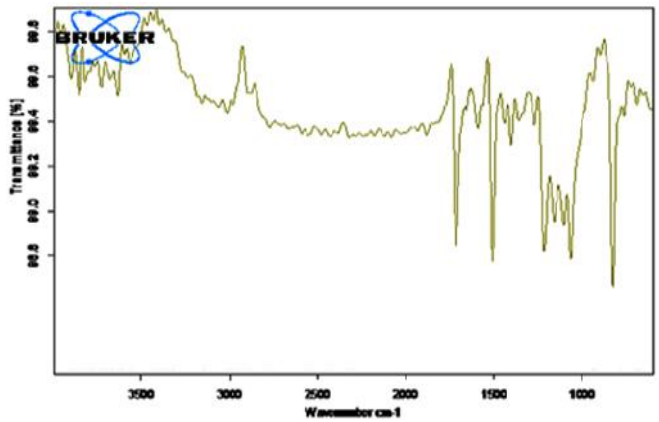

Figure 2: FT-IR spectrum of Ezetimibe + excipients

Precompression evaluation: The results are given in the table 3.

Based on the angle of repose it was observed that all the formulations shown excellent flow property.Bulk density for all the formulations from F1-F10 was in the range of 0.480±0.006 to 0.508±0.038g/cc. Tapped density of all formulations varied from F1 to F10 was in the range of 0.624± 0.002 to 0.652±0.032g/cc. Compressibility index was carried out and found to be between 19.41± 0.15% to24.8± 0.3% it indicate that powder blends have required flow properties for compression. Hausner's ratio was carried out and found to be between 1.23± 0.02 to 1.3 ±0.03 which indicated the powder blends has good flow properties for compression.

Post formulation studies:

Weight variation test: The percentage weight variations for all formulations were tabulated in table-4. All the formulated tablets passed weight variation test, as the % weight variation was within the pharmacopoeia limits

±10% of the average weight. The weights of all tablets were found to be uniform with low standard deviation values.

Hardness test: The measured hardness of tablets of each batch between 5.8 ± 1.97 to 7.2 ± 2.12 Kg/cm² the results shown in table-4. This ensures good handling characteristics of all batches.

Friability test: The values of friability were tabulated. And the values range from 0.3 ± 0.03 to 0.72± 0.065 the percentage friability was less than 1% in all the formulations.

Disintegration test:

The values of disintegration test for Ezetimibe tablets were tabulated in table-4. The results of in-vitro disintegration times of all the tablets were found to be within the prescribed limits and satisfy the criteria of immediate release tablets. Among all the formulations, F7 containing microcrystalline cellulose, croscarmellose sodium and lactose monohydrate showed the highest efficiency i.e., 3.10mins.

Table 1: Different formulation trials of ezetimibe immediate release tablets

Name of the ingredient	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Ezetimibe	10	10	10	10	10	10	10	10	10	10
PGS (starch 1500)	55	-	-	-	-	-	-	-	-	-
Dicalcium phosphate anahydrous (A-Tab)	-	55	-	-	-	-	-	-	-	-
Avicel 101	-	12	62	-	5	5	5	5	5	5
Avicel 102	12	-	-	47	-	-	-	-	-	-
Croscarmellose sodium	5	5	5	5	5	10	10	10	8	10
Sodium lauryl sulfate	2	2	2	2	2	2	2	2	2	-
Colloidal silicon dioxide	-	-	-	-	-	-	2	2	2	2
Lactose monohydrate	-	-	-	15	74.5	69.5	67.5	65.5	69.5	69.5
Binder solution										
Purified water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Povidone k 30	2	2	2	2	2	2	2	4	2	2
Extra granular portion										
Avicel 102	10	10	15	15	-	-	-	-	-	-
Croscarmellose sodium	3	3	3	3	-	-	-	-	-	-
Magnesium stearate	1	1	1	1	1.5	1.5	1.5	1.5	1.5	1.5
Total tablet weight (mg)	100	100	100	100	100	100	100	100	100	100

Table 2: Results of physical compatibility studies at different storage conditions

Composition details	**Initial**	**Storage conditions/duration**				
		40^0C, 75% RH			**60^0C**	
		10 days	**20days**	**30days**	**15days**	**1month**
Ezetimibe	An off white crystalline powder	complies	complies	complies	complies	complies
Ezetimibe : Lactose monohydrate (1:5)	White to off white powder	complies	complies	complies	complies	complies
Ezetimibe: MCC(1 : 1)	White to off white powder	complies	complies	complies	complies	complies
Ezetimibe : CCS(1 : 1)	White to off white powder	complies	complies	complies	complies	complies
Ezetimibe : SLS (1:0.25)	White to off white powder	complies	complies	complies	complies	complies
Ezetimibe : colloidal silicon dioxide (1:0.25)	White to off white powder	complies	complies	complies	complies	complies
Ezetimibe: HPMC(1:0.25)	White to off white powder	complies	complies	complies	complies	complies
Ezetimibe magnesium stearate	White to off white powder	complies	complies	complies	complies	complies

Table 3: Pre compression studies for the prepared granules

Formulation Code	Bulk density Avg ±SD (n =3)	Tapped density Avg ±SD (n =3)	Compressibility index Avg ±SD (n =3)	Hausner's Ratio Avg ±SD (n =3)	Angle of repose (θ) Avg ± SD (n =3)
F1	0.480± 0.006	0.624± 0.002	22.95± 0.07	1.3 0.03	23° .2' ± 0.711
F2	0.484± 0.010	0.628± 0.006	21.08± 0.05	1.29 0.025	22°.4' ± 0.707
F3	0.490± 0.016	0.632± 0.01	22.46 ±0.12	1.28± 0.025	22° ± 0.704
F4	0.492± 0.018	0.628± 0.006	19.60± 0.04	1.27 ±0.03	20°.2' ± 0.698
F5	0.498± 0.024	0.626± 0.004	19.41± 0.15	1.25± 0.03	18°.4' ± 0.65
F6	0..500± 0.025	0.624± 0.002	24.8± 0.3	1.24 ±0.025	19°.6 ' ± 0.68
F7	0.508± 0.038	0.652± 0.032	23.4± 0.28	1.28 ±0.15	19°.2' ± 0.67
F8	0.506± 0.032	0.634± 0.012	20.18± 0.12	1.25± 0.03	20° ± 0.66
F9	0.502± 0.028	0.646± 0.026	22.29± 0.07	1.28± 0.04	18°.24' ± 0.61
F10	0.504± 0.03	0.624± 0.002	24.8± 0.15	1.23± 0.02	19°.2' ± 0.62

Table 4: Post compression parameters for formulations

Formulation code	Weight variation (mg) Avg±SD (n= 20)	Hardness (Kg/cm^2) Avg ± SD (n = 3)	Friability (%)	Disintegration time (min) Avg ± SD (n = 3)
F1	100.1 ± 0.70	7.2 ± 2.12	0.72± 0.065	6' 20" ±0.015
F2	99.8 ± 0.53	7.0 ± 2.2	0.6 ± 0.02	5' 90" ± 0.03
F3	100 ± 0.35	6.8 ± 2.3	0.7 ± 0.01	4'50" ± 0.03
F4	100.16 ± 0.53	6.6 ± 2.42	0.5 ± 0.02	5' 20" ± 0.05
F5	100.83 ± 0.88	6.4 ± 2.56	0.52 ± 0.05	4' 22" ± 0.015
F6	101.5 ± 0.35	6.1 ± 2.62	0.54± 0.03	4' 12 " ± 0.02
F7	101 ± 0.61	5.8 ± 1.98	0.58 ± 0.03	3' 10 " ± 0.03
F8	101 ± 0.61	6.2 ± 2.71	0.4 ± 0.02	3' 10" ± 0.03
F9	101 ± 0.37	6.1 ± 2.61	0.3 ± 0.03	4' 10" ± 0.02
F10	100.16 ± 0.53	5.8 ± 1.97	0.4 ± 0.03	3 '10" ± 0.03

Table 4.10: *In - Vitro* drug release data for formulation F1-F5

Time(min)	Cumulative % drug release				
	F1	F2	F3	F4	F5
5	46.26	53.26	47.66	58.26	79.16
10	68.12	65.12	67.52	76.12	85.24
20	76.15	69.23	76.12	84.58	86.32
30	80.20	71.52	84.26	86.12	88.12
45	82.96	73.51	88.52	87.24	88.24
60	83.12	75.12	89.62	89.68	92.32

Table 4.11: *In- Vitro* drug release data for formulation F6-F10

Time(min)	Cumulative % drug release				
	F6	F7	F8	F9	F10
5	75.82	72.52	52.52	53.12	55.58
10	83.26	91.18	83.12	79.52	80.26
20	85.52	94.52	88.52	88.36	82.12
30	87.62	95.61	89.23	89.52	82.58
45	89.52	95.72	89.32	90.12	83.36
60	94.82	96.5	94.25	90.52	85.92

***In-vitro* dissolution study:**

All the formulations of prepared immediate release tablets of Ezetimibe were subjected to in-vitro release studies using paddle dissolution apparatus in 0.45% SLS in 0.05M acetate buffer P^H 4.5. The dissolution rate was found to increase frequently with increasing concentrations of diluents and disintegrants.

- Formulations F1, F2 and F3 which containing pregelatinized starch, micro crystalline cellulose, croscarmellose sodium, dicalcium phosphate anahydrous, have recorded drug release 83.12%,73.12%, 89.62% respectively within 60min.

- Formulations F4, F5, F6, formulations containing lactose monohydrate, microcrystalline cellulose (Avicel 102), and croscarmellose sodium have recorded drug release 89.68%, 92.32%, 94.52% respectively within 60 min.
- Formulations F7, F8, F9, F10 formulations containing micro crystalline cellulose (Avicel101), lactose monohydrate, croscarmellose sodium have recorded drug release 96.5% , 94.25%, 90.52%, 85.96% respectively within 60 min

4. Conclusion

Ten formulations of immediate release tablets of Ezetimibe were successfully prepared by using various diluents and disintegrants by wet granulation method and were found to be good without chipping and sticking. The tablets were evaluated for precompression parameters and post compression parameters and the results were within the limits. The drug - diluent and disintegranting agents ratios was found to influence release of drug from the formulations. From the in-vitro drug release study of Ezetimibe immediate release tablets it was found that formulation F-7 has shown maximum of 96.5% drug release with in 60 min. thus it is optimized. Formulation F-7 containing increasing concentrations of lactose monohydrate, cross caramellose sodium and microcrystalline cellulose, has shown good release, good hardness, low friability and disintegration time than the other formulations. As the levels of diluents and disintegrating agents increased, the drug release rates were found to be increased.

5. References

1. Ansel`S Pharmaceutical Dosage Forms &Drug Delivery Systems, Eighth Edition, pp: 227-260.
2. Utsav Patel, Khushbu patel, Darshan shah, Rushabh shah. A review on immediate release drug delivery system. IJPRBS, **2012**, 1(5): 37-66.
3. Nyol Sandeep, M.M. Gupta. Immediate drug release dosage form: a review. Journal of Drug Delivery & Therapeutics, **2013**, 3(2): 155-161.
4. Syed azeem, Shaweta Sharma. Immediate release drug delivery systems: A Review. International journal of biopharmaceutical & toxicological research, **2011**, 1(1): 24-46.
5. Jay Garg. Current Status of Drug Delivery Technologies and Future Directions. Pharmaceutical Technology On-Line, **2001**, 25(2): 1–14.
6. Bhowmik D, Chiranjib B, Pankaj K, Chandira RM. Fast dissolving tablets: An overview. Journal of Chemical and Pharmaceutical Research. **2009**, 1(1): 163-772.
7. Vishal G. Rathod1, Vaishali Kadam1, S. B. Jadhav. Immediate release drug delivery system: A Review. World journal of pharmacy and pharmaceutical sciences, **2014**, 3(6): 545-558.
8. Kiran Wale, Kishor Salunkhe, Ishwar Gundecha. Immediate Drug Release Dosage Form: A Review. Am. J. PharmTech Res., **2014**, 4(1): 190-212.
9. Nyol Sandeep, Dr. M.M. Gupta. Immediate Drug Release Dosage Form: A Review. J Drug Delivery & Therapeutics, **2013**, 3(2): 155-161.
10. Rishikesh, Mohiuddin Ahmed Bhuyian, Ms.Irin Dewan, Drishti Rani Ghosh & Md.Asraful Islam. Immediate Release Drug Delivery System (Tablets): An overview. Int. Res J Pharm. App Sci., **2012**, 2(5): 88-94.
11. Garcia-Calvo M, Lisnock J, Bull HG, Hawes BE, Burnett DA, Braun MP. The target of ezetimibe is Niemann-Pick C1-Like 1 (NPC1L1). Proc Natl Acad Sci USA., **2005**, 102 (23): 8132-7.
12. Temel, Ryan E, Tang, Weiqing Ma, Yinyan, Rudel, Lawrence L, Willingham, Mark C, Ioannou, Yiannis A, Davies, Joanna P, Nilsson, Lisa-Mari, Yu, Liqing. Hepatic Niemann-Pick C1-like 1 regulates biliary cholesterol concentration and is a target of ezetimibe J. Clin. Invest., **2007**, Jul 2, 117(7): 1968–1978.
13. DiPiro JT, Talbert RL, Yee GC, Marzke GR, Wells BG, Posey LM. Pharmacotherapy:A pathophysiologic approach. 7th ed. New York: The McGraw-Hill Companies, Inc. **2008.**
14. Lachman L, Liberman HA, Kang JL, Editors. Tablets, In: The theory & practice of industrial pharmacy, **2004**, pp: 475-501.
15. Subrahmanyam CVS. Text book of physical pharmaceutics. 2nd edition, vallabh Prakashan, **2000**: 189-228.
16. K. Deepthi Naidu, Abbaraju Prasanna Lakshmi, Ajay Kumar. B, J.Narandrareddy. Formualtion and Evaluation of conventional tablets of Ezetimibe by using solid dispersions. International Journal of Pharmacy and Pharmaceutical sciences, **2013**, 5(2): 331-335.
17. Nutan Kumari, B. Srivasatva, Ajay Kumar Tiwari, Renu Kalyanwat. Optimization and evaluation of Immediate release tablets in combination of ezetimibe and simvastatin drugs. International Journal of Pharmacy and Natural Medicines, **2013**, 1(1): 01-13.