

Formulation Development and Evaluation of Oro-Dispersible Tablets Based On Solid Dispersion of Cimetidine

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Abstract

The most common problem about conventional dosage form is dysphagia (difficulty in swallowing). So, we design a new approach in a conventional dosage form which is oral dispersible tablet. Oral dispersible tablet is also called as mouth dissolving tablet, fast dissolving tablet, or oral disintegrating tablet. Oral dispersible tablet has advantage as it quickly disintegrates into saliva when it is put on the tongue. The faster the drug disintegrates or is dissolved, the faster the absorption and the quicker the therapeutic effect of drug will be attained. The objective of present study was to formulate directly compressible orodispersible tablets of cimetidine with improved solubility and bioavailability by using solid dispersion technique. Cimetidine is a histamine H₂-receptor antagonist. It is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastroesophageal reflux disease and erosive esophagitis. Solid dispersion of cimetidine was prepared by anti-solvent addition method and physical mixture using novel polymer eudragit E 100. Saturation solubility of drug was determined in physical mixture and solid dispersion formulation. The prepared solid dispersion formulations were further characterized by drug contents, HPLC, and encapsulation efficiency. Orodispersible tablets of cimetidine were prepared by direct compression method and blend was evaluated for the pre-compression parameters such as bulk density, compressibility, angle of repose etc. The tablets were prepared by using selected solid dispersion formulation and excipients with sodium starch glycolate as a superdisintegrant and evaluated for hardness, friability, weight variation, content uniformity, wetting time, dispersion time and *in-vitro* drug release. Orodispersible tablet shows wetting time 27±1 seconds and *in-vitro* drug release 93.20±3.181%, which is better as compare to tablet containing pure drug (82.36±1.986) within 20min. Thus formulation of orodispersible tablet of cimetidine solid dispersion showed increased solubility and bioavailability with patient complies and convenience.

Keywords: Cimetidine, Orodispersible tablets, Solid dispersion, Anti solvent addition method, Superdisintegrant

INTRODUCTION

Limited and variable drug absorption resulting in poor bioavailability is the major problem that can be encountered when delivering an active agent via oral route. Bioavailability of the drug is one critical parameter for determining the efficacy of pharmaceutical formulations^{1, 2}. Drug absorption from GIT can be limited and varied by a variety of factors with most significant contributors being poor aqueous solubility and/or membrane permeability of the drug molecule. The therapeutically effective amount of a medicine in a composition should be made available to the organism, with optimum blood concentrations of the active ingredients reached within the shortest possible time. Since the development cost of a new chemical entity is very high, the pharmaceutical companies are focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects³⁻⁵. Solubility enhancements of poorly water soluble drugs are needed. Solid dispersion technique is extensively used to increase the solubility of poorly soluble drug⁶. For the past two decades,

there has been enhanced demand for more patient compliance dosage forms. As a result, the demand for their technologies has been increasing three-fold annually. Solid dosage forms like tablets and capsules are more popular and preferred drug delivery system because they have accurate dosing, good physical and chemical stability. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients in compliance particularly in case of pediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water⁷. Difficulty in swallowing (dysphasia) is a common problem of all age groups, especially the elderly and pediatrics, because of physiological changes associated with these groups^{8,9}. Other categories that experience problems in using conventional oral dosage forms include the mentally ill, uncooperative and patients suffering from nausea, motion sickness, sudden episodes of allergic attack or coughing. It is estimated that 35-50% of the population is affected by this problems. Recent advances in novel drug delivery systems aim to enhance safety and efficacy of drug molecule by

formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is to enhance the solubility of drug by solid dispersion technique and further to formulate orodispersible tablet⁹. Cimetidine is a histamine H₂ receptor antagonist. It is a specific competitive antagonist of histamine H₂ receptor at the parietal cell¹⁰. It is widely used in condition where inhibition of gastric acid secretion may be beneficial such as heart burn associated with acid reflux, duodenal and gastric ulcer, gastroesophageal reflux diseases and hyper-secretory syndrome such as Zollinger –Ellison's¹¹. Literature shows that cimetidine is poorly absorbed from the lower gastrointestinal tract and has a short elimination half-life. Many patients find it difficult to swallow tablets and hard gelatin capsules and thus not comply with prescription that results in high incidence of non-compliance and ineffective therapy. Orodispersible tablets are gaining prominence as new drug delivery systems. These dosage forms dissolve or disintegrate in oral cavity within a minute without the need of water or chewing before swallowing¹² sodium starch glycolate is used as superdisintegrant in given formulation to achieve fast disintegration of tablet and patient compliance and convenience¹³.

MATERIALS AND METHODS

Materials

Cimetidine was a gift sample from Hetero Drugs Ltd., (Hyderabad, India). Sodium croscarmellose and eudragit E 100 was obtained from Hi-Media Laboratories Pvt. Ltd., Mumbai, India. Talc, mannitol and magnesium stearate was procured from Central Drug House (P) Ltd. New Delhi. All other solvents and chemicals used were of analytical grade.

Methods

Preformulation studies

Standardization of cimetidine by UV-Visible spectrophotometry

Accurately weighed 10 mg of drug was dissolved in 10 ml of 0.1 N HCL solutions in 10 ml of volumetric flask. The resulted solution 1000µg/ml and from this solution 1 ml pipette out and transfer into 10 ml volumetric flask and volume make up with 0.1 N HCL solution, prepare suitable dilution to make it to a concentration range of 2-14µg/ml. The spectrum of this solution was run in 200-400 nm range in U.V. spectrophotometer (Labindia-3000+).

Solubility study by shake flask method

This study is done by using UV spectrophotometric analysis. Excess of pure drug (10 mg) is dissolved in 0.5 ml of 0.1 N HCL and 6.8 PBS in eppendorf tubes. Now placed both the eppendorf tubes in shaker incubator for 30 min. Centrifuged the tubes at 10000 rpm in research centrifuge for 10 min and took 0.1 ml supernatant, diluted it up to suitable volume and took absorbance in UV spectrophotometer. Calculated the solubility by using calibration curve.

Determination of melting point

The melting point is a parameter to judge the purity of crude drugs. In this case of pure chemicals or photochemical, melting point is very sharp and constant. Since the crude drugs contain the mixed chemicals, they are description with certain range of melting point. A small quantity of cimetidine powder was placed in a capillary tube. The tube is placed in the melting point (VEGUS) apparatus. The temperature in apparatus was increased automatically and noted the temperature at which powder started to melt.

Preparation of cimetidine solid dispersion

Solid dispersion of cimetidine was prepared by anti solvent addition method¹⁴ according to the formulae given in Table 1. Dissolve 55mg of eudragit E 100 polymer and 10 mg cimetidine in 0.1N HCL by stirring at low speed. Then, add this above polymer solution in 20 ml of 0.1N NaOH drop wise while stirring. A turbid solution is formed. The above solution is centrifuged at a specific speed. Pellet is formed at the base and supernatant is discarded. Washed the pellet 3 times by suitable solvent to remove unwanted residual solvent. Collected the pellet and dried it in oven at appropriate temperature. Crushed and powdered by mortar pestle. Collected the powder.

Table 1: Composition of solid dispersion of cimetidine

Chemical	Quantity
0.1 N HCL	5 ml
0.1 N NAOH	20 ml
EUDRAGIT E 100	55 mg
CIMETIDINE	10 mg

Characterization of solid dispersion

Determination of production yield

The production yield of all of the solid dispersion was determined by calculating the initial Weight of the solid raw materials and the final weight of the obtained solid dispersion then Calculated according to the equation below:

$$\text{Production yield} = \frac{\text{Practical weight}}{\text{Theoretical weight (polymer + drug)}} \times 100$$

Calibration curve of cimetidine solid dispersion by HPLC

Chromatographic conditions

Wavelength: - 220 nm, Flow rate: - 1.5 ml per minute, Retention time: - 3.864 minute. Pressure: - 206 Kg^f¹⁵.

Procedure

Mobile phase: - 200 ml methanol + 0.3 ml phosphoric acid in 1000 ml water. Mix and filter

Standard preparation: - solvent is methanol: water (1:4).

Dissolve cimetidine to obtain a stock solution having a known concentration of 0.4 mg per ml. this is done by dissolving cimetidine in one part of methanol and diluting with 4 parts of water. Transfer 5 ml of stock to 200 ml volumetric flask, dilute with mobile phase to volume and mix to obtain a solution of 10 mcg per ml. Now, from above stock solution .05 ml is taken and diluted upto 10 ml with solvent. This becomes 2 mcg per ml. Thus, similarly 4, 6, 8, 10 mcg per ml concentrations were made by taking .01ml, .15ml, .20ml, .25ml and diluting up to 10ml by solvent. Then samples are injected in HPLC by 20 micro litre injections. Peak area is obtained and calibration curve is plotted.

Sample injection: - 10 mg powdered solid dispersion sample is dissolved in 0.1 N HCL and water mixture and make up to 10ml. Sonicated and filtered. Then, 1ml of above was taken and makes up to 10 ml by water. Injected and peak area was observed.

Entrapment efficiency

The encapsulation efficiency (EE %) is defined by the concentration of the incorporated material (such as active ingredients) detected in the formulation over the initial concentration used to make the formulation. Encapsulation

efficiency (EE %) was calculated using below formula:
 $EE\% = \text{entrapped drug} / \text{total drug taken} \times 100$

Drug content

Drug content is determined by finding out the amount of entrapped drug in the formulation and dividing it by the total amount of formulation¹⁶.

$$DC = \text{Practical amount} / \text{total amount} \times 100$$

Solubility enhancement determination by shake flask method

Take excess of cimetidine drug in 1 ml of solvent in eppendorf tubes. Place the tube in shaker incubator for 30 min. Centrifuged the tube in research centrifuge for 10 min at 10000 rpm. Collected 0.1 ml supernatant and make up to 10 ml by solvent. Did the further dilutions if necessary. Injected and observed peak in HPLC. Put the values in calibration curve and calculated the solubility¹⁶.

1. Formula-1

$V_1 / \text{standard 1} \times 100$, where V_1 = pure drug peak in 6.8 PBS.

Standard 1 = pure drug standard peak in 0.1 N HCL.

2. Formula-2

$V_2 / \text{standard 2} \times 100$, where V_2 = sample peak in 6.8 PBS.

Standard 2 = sample peak in 0.1 N HCL.

Preparation of oro-dispersible tablets of cimetidine

Oro-dispersible tablets of cimetidine were prepared by direct compression method. The suitable quantity of drug, diluents, superdisintegrants and sweetener was screened through 40 # and properly mixed together. Talc and magnesium stearate was screened through 80 # and blended with initial mixture. Powder thus obtained was compressed into tablets on an 8 station single punch rotary tablet compression machine¹⁷.

Table 2: Formula for oro-dispersible tablets of cimetidine

Ingredients	Quantity
Sodium starch glycolate	7.2mg
Magnesium stearate	2.16mg
Talc	1.24mg
Mannitol	84mg
Drug polymer complex	30mg
Total	124mg

Evaluation of oro-dispersible tablets of cimetidine

Precompression parameters

Angle of repose (θ)

The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} (h/r)$$

Where, θ is the angle of repose, h is the height, r is the radius.

The granules were allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

$LBD (\text{Loose Bulk Density}) = \text{Mass of Powder} / \text{Volume of Packing}$

$TBD (\text{Tapped Bulk Density}) = \text{Mass of Powder} / \text{Tapped Volume of Packing}$

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index.

$$\text{Carr's index (\%)} = [(TBD - LBD) / TBD] \times 100.$$

Hausner's ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula¹⁸.

$$\text{Hausner's ratio} = \text{Tapped density} / \text{Bulk density}.$$

Post compression parameters¹⁹

Thickness variation

Five tablets were taken and their thickness was measured using vernier calipers. The thickness was measured by placing tablet between two arms of the vernier calipers.

Hardness

Hardness or crushing strength of the tested orally disintegrating tablet formulations was measured using the dial hardness tester (Monsanto hardness tester).

Friability

The friability of a sample of 20 orally disintegrating tablets was measured utilizing a USP-type Roche friabilator. Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then de-dusted, reweighed, and percentage weight loss (friability) was calculated by equation:-

$$\% \text{ Friability} = W_0 - W / W_0 \times 100$$

W_0 = initial weight of 20 tablets,

W = weight of 20 tablets after 100 revolution

Wetting time measurement

Five circular tissue papers were placed in a petri dish of 10 cm diameter. The dye solution was used to identify complete wetting of the tablet surface. A tablet was carefully placed on the surface of the surface of the tissue paper in the petri dish at 25°C. The time required for water to reach the upper surface of the tablets. To completely wet them was noted as the wetting time. Wetting time was recorded using stopwatch.

In-vitro dispersibility test

The test is carried out on a tablet in the beaker containing 50 ml 6.8 PBS and the time in second taken for complete dispersion of the tablet is measured.

In vitro dissolution studies

In vitro dissolution studies were performed for the tablets using USP dissolution apparatus II (paddle type), at 50 rpm, thermostatically maintained at temperature $37 \pm 0.5^\circ\text{C}$, with dissolution medium of 500 ml 6.8 PBS. Tablet containing solid dispersion and another tablet containing pure drug are taken in different vessels. Dissolution study was carried out for duration of 30 min with sampling interval of 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes and 30 minutes. The absorbance of test solution measured at 235 nm.

RESULTS AND DISCUSSION

The λ_{max} of cimetidine was found to be 235nm by using U.V. spectrophotometer (Labindia-3000+) in linearity range 2-14 $\mu\text{g/ml}$ Fig 1. Solubility of cimetidine is determined by UV spectrophotometer. Solubility is calculated by putting value of absorbance in calibration curve. Solubility in 0.1 N HCL and in 6.8 PBS was found to be 9.89 and 5.30mg/ml respectively. The melting point of cimetidine was found to be 145°C . Calibration curve of cimetidine by HPLC was found to be linear in the conc range 2-10 $\mu\text{g/ml}$ Fig. 2. HPLC chromatogram of diluted solid dispersion sample in 0.1 N HCL was given in Fig.3, which shows RT of cimetidine 3.864 and peak area 6974. Thus, after calculation by calibration curve, amount of drug found in 10 mg formulation is 0.853 mg. (out of 1.66 mg). % Yield, % entrapment efficiency and % drug content of solid dispersion of cimetidine was found to be 53.84 %, 51.43% and 8.5 % respectively. The results stated that the solubility of pure cimetidine in 6.8 PBS (60 %) is less as compared to solubility of solid dispersion containing drug (92.844 %). thus, it is evident that after the incorporation of drug into solid dispersion, the solubility is enhanced 1.54 times. Tablet powder blend was subjected to various pre-compression parameters Table 3. The angle of repose values indicates that the powder blend has good flow properties. The bulk density, tapped density, compressibility

index and hauser's ratio of the formulation was found to be within the range and showing that the powder has well flow properties. The results of post-compression parameters such as the uniformity of weight, hardness, thickness, friability and wetting time of the tablets are given in Table 4. Thus all the physical attributes of the prepared tablets were found be practically within control. *In-vitro* drug release of tablet was found to be $93.20 \pm 3.181\%$, which is better as compare to tablet containing pure drug (82.36 ± 1.986) within 20min Table 5.

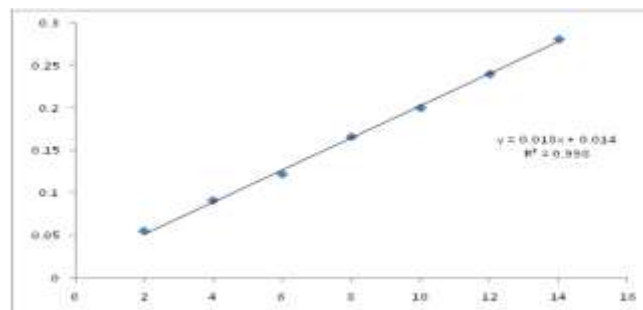


Figure 1: Calibration curve of cimetidine by Uv-Vis spectroscopy

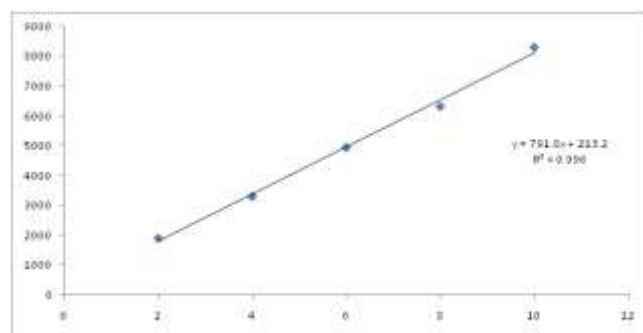


Figure 2: Calibration curve by HPLC

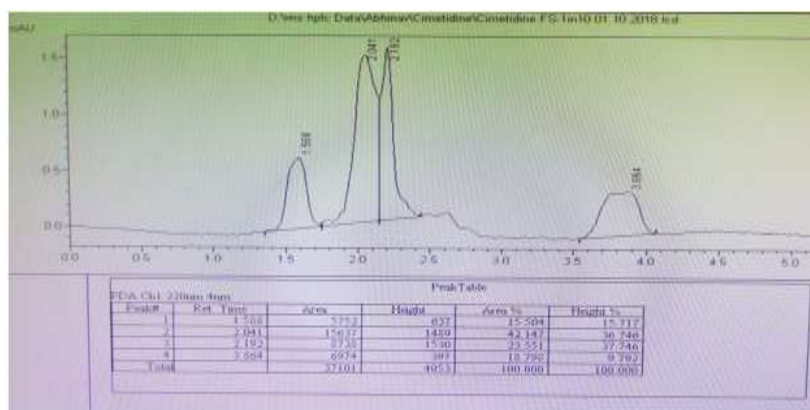


Figure 3: HPLC chromatogram of diluted solid dispersion sample in 0.1 N HCL.

Table 3: Results of pre-compression parameters of formulation

Parameters	Range	Remarks
Bulk density	0.4 ± 0.015	Within limits
Tapped density	0.63 ± 0.017	Within limits
Carr's index	19.20	Fair
Hausner ratio	1.45	Fair
Angle of repose	28.43 ± 1.21	Good flow
Compressibility index	19 ± 1	Fair

Table 4: Results of post-compression parameters of all formulation

Parameters	Range	Remarks
Friability (%)	0.10 ± 0.03	Within limits
Hardness(kg/cm ²)	2.7 – 2.9	Sufficient hard
Thickness (mm)	2 ± 4	
Wetting time (sec)	27 ± 1	Acceptable
Dispersion Time (sec)	31 ± 2	Acceptable

Table 5: %cumulative drug release of cimetidine from ODT

Time(min)	% cumulative drug release of tablet containing solid dispersion	% cumulative drug release of tablet containing pure drug
0	0	0
5	43.49±1.988	34.45±2.992
10	65.26±2.554	53.33±3.212
15	83.02±1.657	69.20±2.865
20	93.20±3.181	82.36±1.986
25	-	-
30	-	-

CONCLUSION

There is bioavailability problem associated with oral drug delivery and also the drawbacks of high dosing of drugs, which leads to toxicity. Thus, an attempt is made in this work to decrease the dose of cimetidine by enhancing solubility by formulating the solid dispersion using anti solvent addition method. Anti solvent addition method is a fast method to prepare solid dispersion of desired size range, and another advantage is the low cost during preparation. It can be concluded that combination of solid dispersion and superdisintegrant is a promising approach to prepare efficient orodispersible tablet of cimetidine (low solubility, high permeability).

REFERENCES

- Das SK, Roy S, Yuvaraja K, Khanam J, Nanda A. Solid dispersions: An approach to enhance the bioavailability of poorly water soluble drugs. *International Journal of Pharmacology and Pharmaceutical Technology*. 2011; 1(1):37-46. <https://doi.org/10.47893/IJPPT.2013.1006>
- Sharma D, Soni M, Kumar S, Gupta GD. Solubility enhancement- eminent role in poorly soluble drugs. *Research Journal of Pharma and Technology*. 2009; 2 (2):220-224.
- Patel T, Patel L, Patel T, Makwana S, Patel T. Enhancement of dissolution of Fenofibrate by solid dispersion technique. *International Journal Research and Pharm Science*. 2010; 1(2):127-132.
- Weuts I, Kempena D, Verreck G, Peeters J, Brewster M, Blaton N. Salt formation in solid dispersions consisting of polyacrylic acid as a carrier and three basic model compounds resulting in very high glass transition temperatures and constant dissolution properties upon storage. *European Journal of Pharmaceutical Science*. 2005; 25:387-393. <https://doi.org/10.1016/j.ejps.2005.04.011>
- Bramhmankar DM, Jaiswal SB, Biopharmaceutics and Pharmacokinetics- A Treatise, Vallabh Prakashan, Second edition, p. 24-30, 314-336.
- Dhirendra K, Lewis S, Udupa N. Solid dispersions: A review, *Pakistan Journal of Pharmaceutical Science*. 2009; 22:234-246.
- Kuchekar BS, Aruagam VA. Review: Fast dissolving tablets. *Indian Journal of Pharmaceutical Education*. 2001; 35:150-152.
- Lindgreen S, Janzon L. Dysphagia: Prevalence of swallowing complaints and clinical findings. *Medical Clinic of North America*. 1993; 77:3-5.
- Bangale GS, Shinde GV, Stephen B. New generation of orodispersible tablets: recent advances and future prospects, *International Journal of Advances in Pharmaceutical Sciences*. 2011; 2:17-28.
- Hall N. A landmark in drug design. *Chemistry in Britain*. 1997; 33(12):25-7.
- Calvo NL, Maggio RM, Kaufman TS. A dynamic thermal ATR-FTIR/chemometric approach to the analysis of polymorphic interconversions. Cimetidine as a model drug. *Journal of Pharmaceutical and Biomedical Analysis*. 2014; 92:90-7. <https://doi.org/10.1016/j.jpba.2013.12.036>
- Bangale GS, Shinde GV, Stephen B. New generation of orodispersible tablets: recent advances and future prospects, *International Journal of Advances in Pharmaceutical Sciences*. 2011; 2:17-28.
- Gandhi BR, Mundada AS, Gandhi KR, Evaluation of Kyron T-314 (polacrillin potassium) as a novel superdisintegrant, *International Journal of Drug Delivery*. 2011; 3:109-114. <https://doi.org/10.5138/ijdd.2010.0975.0215.03060>
- Jain P, Nair S, Jain N, Jain DK, Jain S. Formulation and evaluation of solid dispersion of lomefloxacin hydrochloride. *International Journal of Research in Pharmaceutical Sciences*. 2012; 3(4):604-608.
- U.S. Pharmacopoeia-National Formulary [USP 39 NF 34]. Volume 1. Rockville, Md: United States Pharmacopeial Convention, Inc; 2014. [1151]
- Masilamani K, Ravichandiran V. Effect of formulation and process variables on drug content and entrapment efficiency of aceclofenac nanosuspension. *International Research Journal of Pharmacy*. 2012; 3 (3):315-318.
- Kuchekar BS, Badhan AC, Mahajan HS. Mouth dissolving tablets of salbutamol sulphate: A novel drug delivery system. *Indian Drugs* 2004; 41:592-8.
- Pandey SP, Khan MA, Dhote V, Dhote K, Jain DK. Formulation development of sustained release matrix tablet containing metformin hydrochloride and study of various factors affecting dissolution rate. *Scholars Academic Journal of Pharmacy*. 2019; 8(3):57-73.
- Patel AK, Rai JP, Jain DK, Banweer JI. Formulation, development and evaluation of cefaclor extended release matrix tablet. *International Journal of Pharmacy and Pharmaceutical Sciences*. 2012; 4(4):355-7.