IJPSR (2015), Vol. 6, Issue 10 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 07 April, 2015; received in revised form, 22 June, 2015; accepted, 29 July, 2015; published 01 October, 2015

DESIGN AND DEVELOPMENT OF FAST DISSOLVING TABLETS OF HYDROCHLOROTHIAZIDE AND ATENOLOL CO-CRYSTALS

Omkar S. Bhandwalkar *, Madhavi U. Bhandwalkar, Dhairysheel M. Ghadge, Pallavi S. Dhekale, Ujwala K. Jamdade

Gourishankar Institute of Pharmaceutical Education and Research, Limb, Satara, Maharashtra, India

Keywords:

HCT, ATL, Solvent evaporation, Solution co-crystallization, Characterization.

Correspondence to Author:
Omkar S. Bhandwalkar
Gourishankar Institute of Pharmaceutical Education and Research, Limb, Satara, Maharashtra, India

E-mail: omkargurav4442@gmail.com

ABSTRACT: Hydrochlorothiazide (HCT) is a class IV drug which has limited solubility and permeability, for overcome this problems co-crystallization method is used. Co-crystallization is the process to enhance the physical properties of drug molecule especially the solubility. HCT belongs to diuretic category and Atenolol (ATL) belongs to Beta blocker category they are combined for use in tablet formulation. Co-crystallization was used to combine two drugs in single solid phase and thus to achieve new approach for combination therapy to treat hypertension. Using the new approach co-crystals of ATL with HCT was prepared. Co-crystallization of two drugs were carried out by using solvent evaporation and solution co-crystallization method. The saturation solubility was done to evaluate the solubility of co-crystals. Comparative drug release study was carried out between co-crystals and marketed formulation. The prepared co-crystals have shown several times faster release than marketed tablet and co-crystals were characterized by using DSC, FTIR and SEM.

INTRODUCTION: Hydrochlorothiazide (HCT) is a diuretic agent, chemically described as a 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide, which is widely used in antihypertensive pharmaceutical preparations, which reduce sodium reabsorption and peripheral vascular resistance. Its molecular formula is $C_7H_8ClN_3O_4S_2$ having molecular weight 297.74 g/mole. It is insoluble in water, freely soluble in methanol, soluble in diluted ammonia or sodium hydroxide.[1]

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.6(10).4368-74

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(10).4368-74

According to the Biopharmaceutical Classification System (BCS) aqueous solubility and permeability are the most important properties affecting drug bioavailability. HCT is classified in Class IV, where the drugs have low solubility and low permeability characteristics after oral administration [1, 2].

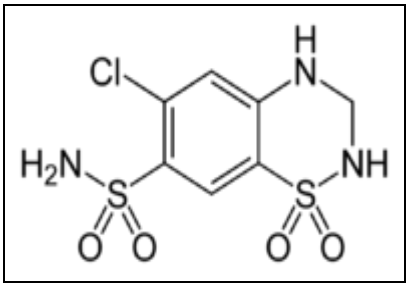

FIG. 1: CHEMICAL STRUCTURE OF HYDROCHLOROTHIAZIDE

Atenolol is a β_1 selective drug and widely used in treatment of cardiovascular diseases. It is

chemically described as benzene acetamide, 4-[21-hydroxy-31-[(1-methyl ethyl amino] propoxy]. Its molecular formula is $C_{14}H_{22}N_2O_3$having molecular weight 266.34 gm/mole [2].

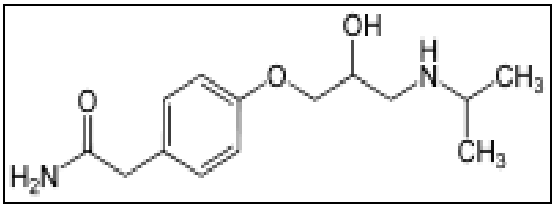

FIG. 2: CHEMICAL STRUCTURE OF ATENOLOL

The concept of co-crystallization constitutes a selective route to the concerted design of pharmaceutical compounds with desired pharmacokinetic and physical properties. The term "co-crystals" is not easily defined but is most commonly used in order to describe a crystal containing two or more components that form a uniform phase. A more refined definition describes a co-crystal as a "multicomponent crystal that is formed between two compounds that are solids under ambient conditions, where at least one component is a neutral API and the co-crystal former is a pharmaceutical acceptable ion or molecule.

In early studies, Etter and co-workers proposed several "hydrogen bond rules," including the observations that all good proton donors and acceptors are used in hydrogen bonding, and the best donor typically pairs with the best acceptor in a given crystal structure. The combined use of the hydrogen-bond rules with a geometric analysis assisted Etter and co-worker in implementing rational design of co-crystals in the synthesis of many new supramolecular structures [3,4].

Co-crystal is crystalline entity formed by two different or more molecular entities where the intermolecular interactions are weak forces like hydrogen bonding and π-π stacking. The concept of modifying the properties of a drug molecule by forming a pharmaceutical co-crystal containing single APIs and a pharmaceutical relevant co-former with improved properties compared with the pure drug crystal has generated immense interest. Physicians prescribe combination therapy frequently to treat and manage a plethora of medical conditions. Multi-API co-crystals, relatively unexplored solid forms of APIs, have potential relevance in the context of combination drugs for pharmaceutical drug development [5].

The design of co-crystals seems to be straight forward because donor and acceptor functionalities can be brought together more easily than with single component systems since the partners are more accessible to arrange themselves into an optimal geometry, leading to favorable intermolecular interactions. Using O-H...N interactions and also N-H…O, one can produce numerous co-crystals from di-acids, alcoholic groups and nitrogen containing aromatic ring and some other compounds. In the absence of strong hydrogen bridges, also, much weaker intermolecular interactions such as C-H…X(X=O,N) can also be used alone to form molecular complexes. Formation of co-crystals may lead to increase in solubility of Hydrochlorothiazide.

Conventional HCT-ATL tablets are available in market are not suitable where quick onset action required. Besides, the conventional tablets also show poor patient compliance particularly by geriatric patients. As the patients with sudden increase blood pressure and acute angina attack, have markedly reduced functional ability and extremely restless, in such cases rapid onset of action is prime importance. So the patients would be benefited from acute treatment by using proposed drug delivery system. This may help them to return to normal state and resume their functional activities. To provide the patients with the most conventional mode of administration, there was need to develop rapidly disintegrating dosage form [6].

MATERIALS AND METHODS:

Materials

Hydrochlorothiazide and Atenolol was received as a gift sample from the Okasa Pharma Pvt. Ltd., Satara, Maharashtra, India. Other chemicals and solvents were obtained from different commercial suppliers.

Preparation of co-crystals:

1. Solvent evaporation method: [7, 8, 9] Taken 10 ml of Ethanol in beaker and placed it on magnetic

stirrer. Then added 1 gm. of Atenolol in that beaker and was stirred for 5 minutes after that added 1 gm. of Hydrochlorothiazide in that solution and the resulting mixture was stirred on magnetic stirrer for 3 hours at 50 rpm. Ethanol was removed by evaporation at room temperature and co-crystals were obtained.

2. Solution co-crystallization: [8]

Taken 10 ml of Ethanol in beaker and heated on water bath at temp.50 to 55°C. Then added equimolar ratio (1:1) of Hydrochlorothiazide and Atenolol in that beaker until it saturates. The Ethanol was removed by evaporation at room temperature and co-crystals were obtained.

Methods of Characterization of Co-Crystals:

1. Saturation solubility study: [8]

Solubility studies were performed according to the method reported by Higuchi and Connors. Excess of pure drug and prepared co-crystals were added to 10 ml of distilled water taken in stopper conical flasks and shaken for 24 hours in rotary flask shaker at room temperature. After shaking to achieve equilibrium, appropriate aliquots were withdrawn and filtered through Whatmann filter paper no. 41 and was analyzed by UV spectrophotometer (Lab India).

2. FTIR Spectroscopy:

FTIR spectra of HCT-ATL co-crystals were obtained by Attenuated Total Reflectance (ATR Bruker Alpha). IR spectrum of drug was recorded as potassium bromide pellet at a resolution of $4cm^{-1}$ over a range 4000-650 cm^{-1}.

3. Differential Scanning Colorimetry:

DSC of HCT-ATL co-crystals done using SDT Q600 V20.9 Build 20 at heating rate of 10°C/min between 0-300°C under nitrogen flow. Accurately weighted samples were placed in sealed aluminium before heating under nitrogen flow.

4. Scanning Electron Microscopy:

The SEM of HCT-ATL co-crystals were carried out to determine the external morphology. The sample was mounted directly on to the SEM sample holder using double sided adhesive tape images were recorded at the required magnification using SEM (JEOL 5400, Japan).

5. Dissolution Rate Study:

Dissolution were performed according to the Dissolution tester (USP Type II) in 900 ml of 0.1 N Hydrochloric acid at the thermostatically controlled temperature of 37°C ± 0.5°C and stirred at 50 rpm. At various time intervals, samples were collected, filtered and analyzed by UV Spectrophotometer (Lab India) at wavelength 272nm.

Formulation of Fast Dissolving Tablets:

For the formulation of fast dissolving tablets 2^2 factorial design is used and 4 batches are formulated and 2 levels are taken (- as 4%) and (+ as 6%) for Crospovidone and Sodium Starch Glycolate.

TABLE 1: FORMULATION OF FAST DISSOLVING TABLETS (mg)

Batches	ATL-HCT	Crospovidone	SSG	Starch	Talc	Mg. Stearate	Avicel 102	Total
F1	50+25	8	8	30	11	6	61	200
F2	50+25	8	12	30	11	6	57	200
F3	50+25	12	8	30	11	6	57	200
F4	50+25	12	12	30	11	6	53	200

RESULTS AND DISCUSSION:

1. Melting point determination: [10] Melting point of the drug sample and co-crystals were determined by open capillary method by using melting point apparatus and found to be shown in table.

TABLE 2: MELTING POINT OF ATENOLOL, HYDROCHLOROTHIAZIDE AND CO-CRYSTAL

Sample	Standard Melting Point (°C)	Observed Melting Point (°C)
Atenolol	146-148	146-148
Hydrochlorothiazide	273-275	273-275
Co-crystal	-	137-138

2. FTIR analysis:

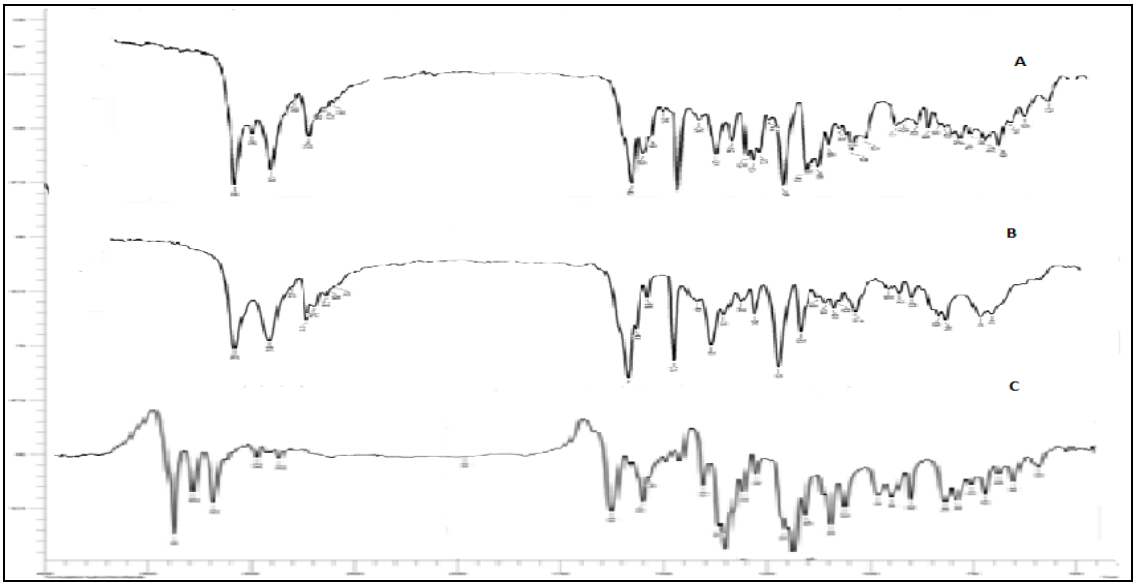

FIG. 3: FTIR SPECTRA OF A- HCT-ATL CO-CRYSTALS, B-ATL, C-HCT.

The IR spectra of HCT and ATL are shown in figure. The IR spectroscopy has also been used to assess the interaction between guest and ATL at shifts or changes in absorption spectra. The IR spectrum of HCT showed an absorption band at 3360.00 cm-1, 3263.56 cm-1, 3163.26 cm-1 due to NH stretching, 1597.06 cm-1 stretching of C=C aromatic ring, 1330.88 cm-1 showed C-N stretching and 1371.39 cm-1 showed SO2 is stretching.[11,12] The IR spectrum for pure ATL shows 3350.35 cm-1 broad peak of (free –OH, stretching), 3163.26 cm-1 (-NH stretching primary and secondary amines), 1637 cm-1 amide.[6]

From FTIR graph of drug and co-crystal there was a shifting of –OH, -NH, C=C aromatic ring, C-N stretching, SO2 stretching peaks towards 3356.14 cm-1, 3265.49 cm-1, 1606.70 cm-1, 1332.51 cm-1, 1373.32 cm-1. This was due to formation of hydrogen bond between drug and co-crystal former. So it was concluded that co-crystals might have formed.

3. DSC analysis:

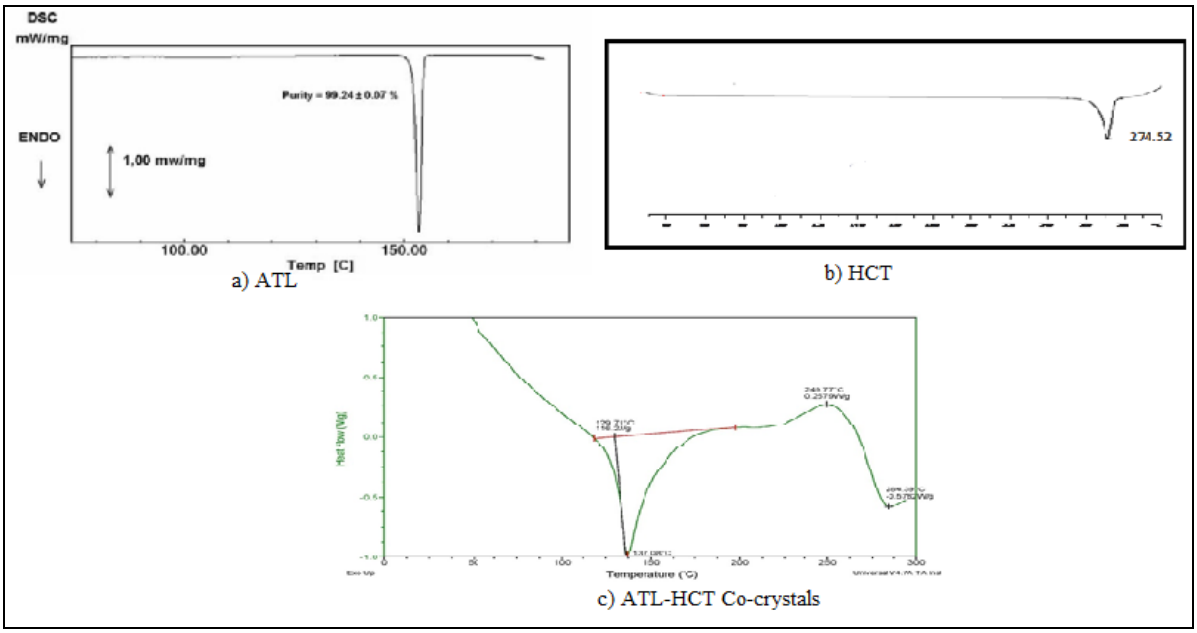

FIG. 3: DSC OF a) ATL, b) HCT and c) ATL-HCT Co-crystals

DSC thermogram of HCT-ATL co-crystal was recorded by using a Differential Scanning Colorimetry with computerized data. HCT and ATL had shown a single endothermic peak maxima at 268.12°C and 152°C due to melting of drug. [6, 13] The thermal behavior of HCT-ATL co-crystal had shown 137.08°C sharp peak for ATL and for HCT 284.39°C which shows shifting of peaks due to the melting of co-crystals. ATL and HCT were found to be below the melting point of co-crystal former. Single endothermic transitions for co-crystal indicates absence of unbounded or absorbed solvent or water and also demonstrate the stability of the phase until melting point.

4. SEM analysis:

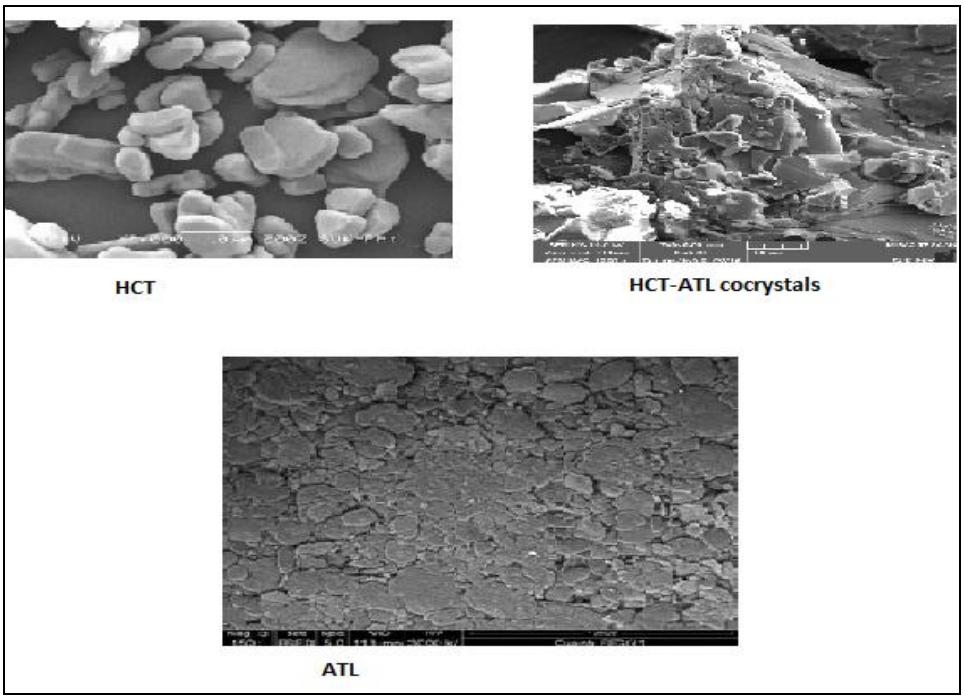

FIG. 5: SEM OF HCT, HCT-ATL CO-CRYSTALS AND ATL

The Scanning Electron Microscopy performed for HCT, ATL and Co-crystals of HCT-ATL. SEM was used to determine surface morphology of the drug and co-crystal. HCT had shown irregular stone shaped crystals.[11, 12] ATL showed smooth surface morphology.[14] SEM of HCT-ATL co-crystal indicated large irregular shaped crystals. From above SEM images we might be concluded that there is change in surface morphology and formation of HCT-ATL co-crystals.

Preformulation Study: [15] The Bulk (BD) and Tapped (TD) densities, Angle of repose, Compressibility index, Hausner's ratio were measured and are shown in table. From the values of compressibility index, Hausner's ratio and Angle of repose it was concluded that co-crystals prepared by above methods showed good flow properties and compressibility.

1. Angle of Repose:

It was determined by fixed funnel method and was calculated by using the formula.

$$\text{Angle of Repose } (\theta) = \tan^{-1} h/r$$

Where, h-height of the cone and r-diameter of the cone.

2. Bulk Density:

Density apparatus was used to determine bulk volume.

Bulk Density = Mass of the powder (w)/ Bulk volume (Vb).

3. Tapped Density:

The tapped density apparatus was set to 100 taps per minute.

Tapped Density = Weight of powder / Bulk density.

4. Hausner's Ratio:

It was calculated from bulk density and tapped density.

Hausner's Ratio = Tapped density / Bulk density.

5. Compressibility Index (%):

It was calculated from bulk and tapped density.

Compressibility Index (%) = Tapped density-Bulk density/Tapped density × 100.

TABLE 3: FLOW PROPERTIES OF CO-CRYSTALS

Physical Parameters	F1	F2	F3	F4
Angle of Repose	25.72	27.54	28.22	26.78
Bulk Density (gm/ml)	0.26	0.24	0.24	0.25
Tapped Density (gm/ml)	0.30	0.32	0.31	0.30
Hausner's Ratio	1.15	1.33	1.29	1.20
Compressibility Index (%)	13.33	22.58	22.45	16.66

Post Compressional Evaluation: [16]

TABLE 4: POST COMPRESSIONAL VALUES

Parameters	F1	F2	F3	F4
Weight variation	200.2	198.7	199.2	197.3
%Friability (%)	0.73	0.98	1.25	1.1
Hardness (kg/cm2)	4.1	4	3.9	4.2
Thickness (mm)	82	83	82	82

Dissolution Rate Studies:

The In Vitro drug release profile of the batches with different superdisintegrant levels is given in table. The rate of *in vitro* drug release was found to be increased. The batches formulated with same concentration of superdisintegrants were shown better drug release.

TABLE 5: % DR OF BATCHES

Time (min)	F1	F2	F3	F4	Marketed
0	0	0	0	0	0
2	**37.65**	6.75	9.25	24.18	5.23
5	69.12	13.50	14.65	53.43	8.24
10	58.32	21.00	17.43	**61.21**	12.55
15	56.45	24.75	21.93	57.15	13.78
20	53.56	25.31	23.06	54.25	15.75
25	52.36	30.93	**23.62**	52.23	19.68
30	50.14	**48.93**	16.87	48.78	35.25
40	48.33	24.75	15.75	45.28	43.20
50	47.01	22.50	12.93	42.89	56.25
60	46.25	21.37	12.37	41.56	**62.43**

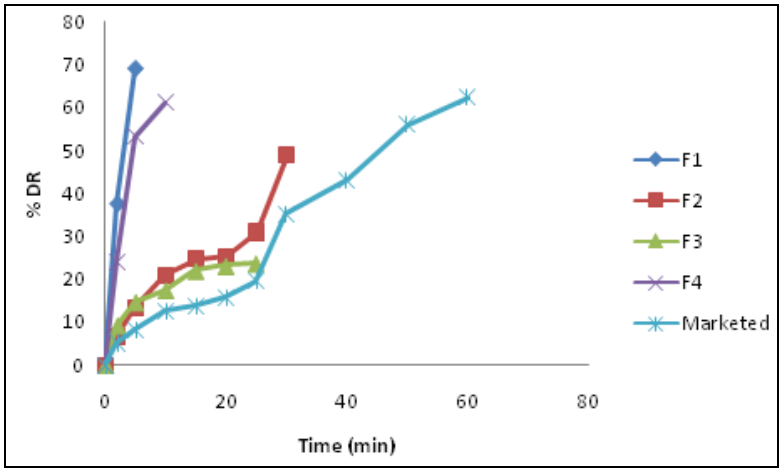

FIG 6: COMPARATIVE *IN VITRO* DRUG RELEASE

CONCLUSION: Co-crystals of HCT-ATL was successfully formed using solvent evaporation and solution co-crystallization methods. This can be proved through their characterization using IR, DSC and SEM. The study successfully demonstrates that co-crystals have shown increased solubility, flow properties and compressibility. The advantages of fast dissolving tablet will surely enhance the patient compliance, low dosing, rapid onset of action and fewer side effects. From the study, it can be concluded that using super disintegrates in tablets showed better disintegration and drug release as compared to normal tablet.

ACKNOWLEDGEMENT: We are thankful to our Institute Gourishankar Institute of Pharmaceutical Education and Research, Limb, Satara for providing necessary facilities to carry out research work and also thankful to Okasa Pharma Pvt. Ltd., Satara for providing gift samples of drugs.

REFERENCES:

1. Drug bank (Hydrochlorothiazide) http://www.drugbank.ca/drugs/DB00999.
2. Drug bank (Atenolol) www.drugbank.ca/drugs/DB00335
3. Blagden N, De Matas M, Gavan PT, York P.: Crystal Engineering of Active Pharmaceutical Ingredients to Improve Solubility and Dissolution Rates. Advanced Drug Delivery Reviews 2007; 59(7): 617-30.
4. Fleischman SG, Kuduva SS, McMahon JA, Moulton B, Bailey-Walsh RD, Rodriguez-Hornedo N et al.: Crystal Engineering of the Composition of Pharmaceutical Phases: Multiple-Component Crystalline Solids Involving Carbamazepine. Cryst Growth and Design 2003; 3(6): 909-19.
5. Sekhon B S: Drug-drug co-crystals. DARU Journal of Pharmaceutical Sciences, 2012, 20:45.
6. Khirwadkar P and Dashora K: Formulation and evaluation of fast dissolving tablets of atenolol. Journal of Chemical and Pharmaceutical Sciences2013; Volume 6(2) 113-118.
7. Pathak CD, Savjani KT, Gajjar AK and Savjani JK: Co-ceystal formation of paracetamol with indomethacin and mefenamic acid: An efficient approach to enhance solubility. International Journal of Pharmacy and Pharmaceutical Sciences 2013; Volume 5(4), 414-419.
8. Narendra Chandel: Cocrystallization of aceclofenac and paracetamol and their characterization. International Journal of Pharmacy and Life Sciences 2011; Volume 2(8), 1020-1028.
9. Setyawan D, Sari R, Yusuf H and Primaharinastiti R: Preparation and characterization of artesunate – nicotinamide co-crystal by solvent evaporation and slurry method. Asian Journal of Pharmaceutical and Clinical Research2014; Volume 7, Suppl 1, 62-65.
10. Zalte AG, Darekar AB, Gondkar SB and Saudagar RB: Preparation and characterization of ibuprofen co-crystals by using solvent evaporation method. World Journal of Pharmaceutical Research 2014; Volume 3(4), 1392-1402.
11. Pires MA and Sinistera RD: Pharmaceutical composition of Hydrochlorothiazide: β-Cyclodextrin: Preparation by three different methods; Physicochemical characterization and In Vivo Diuretic Activity Evaluation2011; Molecules; 4482-4499.
12. Patil JS, Pandya NR, Marapur SC and Shiralashetti SS: Influence of method of preparation on physicochemical properties and in vitro drug release profilr of nimodipine-cyclodextrin inclusion complexes: A comparative study. International Journal of Pharmacy and Pharmaceutical Sciences 2010; Volume 2(1), 71-81.
13. Pereira RN, Bruno RV, Cruz AP, Foppa T, Murakami FS and Silva AS: Thermoanalytical study of atenolol and commercial tablets. Latin American Journal of Pharmacy 2007; 26(3), 382-6.
14. Madaan S, Gupta AK and Sardana V: Improvement in taste and solubility of atenolol by solid dispersion system. The Pharma Innovation 2012; Volume 1, No. 8, 43-49.
15. More HN, Hajare AA: Practical Physical Pharmacy. Career Publication, Edition 3, 126-129.
16. Indian Pharmacopoeia 2010; Volume 1; 189-193.

How to cite this article:
Bhandwalkar OS, Bhandwalkar MU, Ghadge DM, Dhekale PS and Jamdade UK: Design and Development of Fast Dissolving Tablets of Hydrochlorothiazide and Atenolol Co-Crystals. Int J Pharm Sci Res 2015; 6(10): 4368-74.doi: 10.13040/IJPSR.0975-8232.6(10).4368-74.