International Journal of Pharmacy and Natural Medicines
CODEN (USA): IJPNRC | ISSN: 2321-6743
Journal Home Page: www.pharmaresearchlibrary.com/ijpnm

Research Article

Formulation, Development and Evaluation of Voriconazole Immediate Release Tablets

E. Vijay Kumar*, Kandukuri Sai[1], K.S.Shoheb[2], K. Usha Rani[3], K. Supritha[4]

*Associate Professor, Srinivasa Institute of Pharmaceutical Sciences, Proddatur, A.P, India
[1,2,3,4]Srinivasa Institute of Pharmaceutical Sciences, Proddatur, A.P, India

ABSTRACT

In this present study, the tablets were prepared by using wet granulation technique. In order to optimize the product, different formulations were developed. All the formulations were evaluated for physical characteristics, Disintegration, *in-vitro* Dissolution and Stability studies. Based on the results of the above-mentioned tests **Trial F – 08** was selected as the best formulation. Stability studies were performed for this batch for 1 and 3 months under accelerated and long-term testing conditions. Finally, after the duration, the product was analyzed for physical appearance, Hardness, Thickness, Friability, Loss on drying, disintegration, Assay and Related substance. The results obtained were found to be with in the specified limits. The bigger scale confirmatory batch is under 6 months Accelerated stability condition, based on the result, a pilot scale will be executed. After passing the above tests, the in-vivo studies (BA/BE Studies) will be executed to correlate the bioequivalence of best formulation (**Trial F – 08)** with the reference drug.

Keywords: drying, disintegration, Friability, in-vivo studies

Article Info

Corresponding Author
E. Vijay Kumar
Associate Professor,
Srinivasa Institute of Pharmaceutical Sciences, Proddatur, A.P, India

ARTICLE HISTORY: Received 05 June 2023, **Accepted** 07 July 2023, **Available Online** 16 Sept 2023

Citation: *E. Vijay Kumar, et al.* Formulation, Development and Evaluation of Voriconazole Immediate Release Tablets**.** *Int. J. Pharm. Natural Med.,* 2023, 11(1): 31-39.

CONTENTS

1. Introduction. 31
2. Materials and Methods. 33
3. Results and Discussion. 34
4. Conclusion 37
5. References. 38

1. Introduction

Immediate-Release Preparations:

- 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.

- 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 super-disintegrants, such as sodium starch glycolate, croscarmellose 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 and controlled temperature, and freeze-drying.

Ideal Properties of Immediate release dosage forms

They should have

- It should dissolve or disintegrate in the stomach within a short period In the case of solid dosage.
- Should show first absorption and dissolution of drug.
- Rapid onset of action always seen with immediate release tablets.
- Must be compatible with taste masking.
- Be portable without fragility concern.
- It should not leave minimal or no residue in the mouth after oral administration.
- Provides pleasing mouth feel.
- Exhibit low sensitivity to environmental condition as humidity and temperature.
- Be manufactured using conventional processing and packaging equipment at low cost.

Unsuitable drug characteristic for immediate release tablets:

- Drug is not suitable for immediate release tablets which having short biological half-life.
- Drug with low bioavailability is also not desirable candidate for immediate release tablets.
- Drug with higher clearance and higher elimination half-life are also not desirable candidate for immediate release tablets.

Technology for Immediate release Tablets:

Conventional Techniques Conventional technique used in the preparation of immediate release tablets

* Tablet molding technique
* Direct compression technique
* Granulation technique
* Mass extrusion technique

EXCIPIENT PROFILE:

MICROCRYSTALLINE CELLULOSE: Adsorbent, suspending agent, tablet and capsule diluent, tablet disintegrant.

STARCH, PREGELATINIZED: Tablet and capsule diluent, tablet and capsule disintegrant; tablet binder.

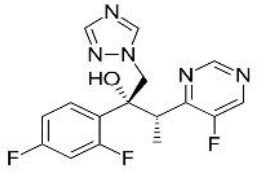
HYDROXYPROPYL CELLULOSE: Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

LACTOSE, MONOHYDRATE: Dry powder inhaler carrier; lyophilization aid; tablet binder; tablet and capsule diluent; tablet and capsule filler.

CARBOXYMETHYLCELLULOSE CALCIUM: Emulsifying agent; coating agent; stabilizing agent; suspending agent; tablet and capsule disintegrant; viscosity-increasing agent; water-absorbing agent.

MAGNESIUM STEARATE: Tablet and capsule lubricant**.**

Table.1: Drug profile

S.No	Physiochemical Nature	Description
1	Common Name	Voriconazole
2	Nature	Prodrug
3	State	Solid
4	Colour	White to off white
5	Taste	Sour to bitter
6	IUPAC Name	(2R,3S)-2-(2,4-Difluorophenyl)-3-(5-fluoropyrimidin-4 -yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol
7	Molecular Formula	$C_{16}H_{14}F_3N_5O$
8	Chemical Structure	
9	Molecular Weight	349.311 g/mol
10	Melting Point	163^0C

11	Solubility	Low soluble in water. It is soluble to the degree of one part in two parts of water and one part in 100 parts of ethanol. It is insoluble in chloroform, acetone, Methylene chloride and ether.
12	Indication	invasive aspergillosis and candidiasis and fungal infections

2. Materials and Methods

Methods:

PREFORMULATION STUDIES:

The API was tested for the following properties:

- Organoleptic Properties
- Solubility
- Water Content
- Particle Size determination
- Drug – Excipient compatibility study
- Flow Properties
  - ❖ Angle of Repose
  - ❖ Bulk Density
  - ❖ Tapped Density
  - ❖ Carr's Index
  - ❖ Hausner's Ratio

Formulation of voriconazole tablets:

Formulation Planning:

The immediate release tablets containing Voriconazole based on the results of preformulation studies; to improve the flow properties tablets were prepared by Wet Granulation Technique and the composition are given in Table 1. Based on Literature survey and Compatibility Tests excipients like Microcrystalline Cellulose (pH 101, PGS, Hydroxypropyl cellulose, Carboxy Methyl Cellulose, Magnesium stearate were used.

EVALUATION OF FORMULATION:

Evaluation of granules:

- Flow Properties:
- Micromeretic properties

Evaluation of tablets:

- Weight variation
- Tablet thickness
- Hardness
- Friability (%):
- Disintegration Test
- *In-vitro* Dissolution Release study

Dissolution conditions:

Medium	:	0.1 N Hcl (pH 1.2)
Volume	:	900ml
Temperature	:	$37^{o}C \pm 0.5^{o}C$
Apparatus	:	USP type –II (paddle)
RPM	:	100
Time interval	:	10, 20, 30, 45 and 60 min

Table.1 List of Materials Used In The Formulation

S.No	Ingredients	Source
1.	Voriconazole	Aurabindo Pharmaceutical co.ltd
2.	Lactose Monohydrate	Avon organics Ltd
3.	PG Starch	SD Fine Chemicals ltd
4.	Microcrystalline cellose (Avicel PH 101)	SD Fine Chemicals ltd
5.	Klucel – LF	SD Fine Chemicals ltd
6.	Ca. CMC	SD Fine Chemicals ltd
7.	Mg. Stearate	SD Fine Chemicals ltd

Table.2. List of Equipments Used for the Formulation

Name of instrument	Model no.	Make
Electronic Weighing Balance	PR 203	Mettler Toledo
Tap Density Tester USP	ETD-1020	Electrolab
Electromagnetic Sieve Shaker	EMS-8	Electrolab
Electronic Moisture Analyzer	HG 63	Mettler Toledo
Tablet Compression Machine-8 station	MINI Press - II MT	Rimek
Digital Hardness Tester	TH 10503	Labindia
Disintegration Test Apparatus USP	ED-2AL	Electrolab
Friabilator USP	EF-2	Electrolab

Mechanical Stirrer	RQT-124D	Remi Motors
Pharma R&D Coater	Deluxe	Ideal Cures
Fluid Bed Drier	UT-150	Umang Pharmatech
Rapid mixture granulator	RMG 25	Anchormark
Multi Mill	MM 15	Anchormark
Weighing balance	T-26I	Scaletec Instruments (Citizen)
Tray Drier	PPT TD6	Platinum Pharmatech
Dissolution Test Apparatus Type II	UV-Pharmaspec – 1700	DBK Instruments Ltd., Mumbai.

3. Results and Discussion

Table.3. Results of physical characterization of the drug

S.No:	Description	Result
1.	Appearance	White to off-white powder
2.	Odour	Characteristic odour.
3.	Solubility	low soluble in water. It is soluble to the degree of one part in two parts of water and one part in 100 parts of ethanol. It is insoluble in chloroform, acetone, Methylene chloride and ether.

*The above result shows that physical characterization of the drug candidate (API) complies with the USP specifications

Table.4. Results of flow properties

S.No	Flow Properties	Result
1	Bulk density (g/ml)	**0.581**
2	Tapped density (g/ml)	**0.714**
3	Carr's index (%)	**18.62**
4	Hausner's ratio	**1.22**
5	Angle of repose	**$22^{o}.8^{I}$**

*From the above results, it is found that the API has **"fair"** flow properties.

Table.5. Compatibility studies

Excipients	% known impurities			% Unknown impurities			Total impurities		
	I	II	III	I	II	III	I	II	III
Lactose	0.15	0.2	0.3	0.01	0.02	0.04	0.4	0.6	0.8
PG Starch	0.1	0.12	0.3	0.02	0.05	0.09	0.1	0.3	0.5
HPC	0.2	0.25	0.35	0.02	0.04	0.08	0.2	0.3	0.6
Ca CMC	0.2	0.18	0.28	0.01	0.04	0.05	0.3	0.5	0.9
Mg.Stearate	0.1	0.15	0.18	0.03	0.04	0.05	0.2	0.3	0.5

Compatibility studies results:

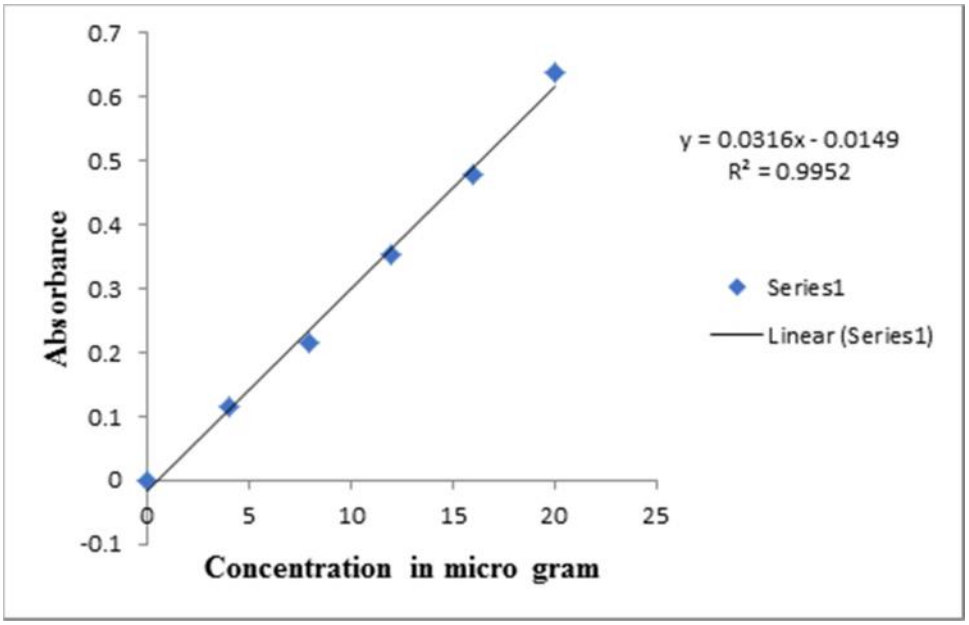
I = Initial
II = Long Term (28 DAYS)
III = Accelerated (14 DAYS)

*No Characteristic change in the color of the powder and no additional degradation of the product was observed.

Table.6. Standard Calibration Curve of Voriconazolein 0.1N HCl:

Concentration (µg/ml)	Absorbance (nm)
0	0
4	0.116
8	0.217
12	0.353

16	0.480
20	0.638



FORMULATION TRIALS:

The Immediate Release tablets of Voriconazole has been formulated and the formula is shown in the below table.

Table.7. Formulation Trials - Formula

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10
Voriconazole	200	200	200	200	200	200	200	200	200	200
Lactose Mono Hydrate	119.8	110.8	95.8	105.8	108.8	92.8	92.8	120.8	107.8	103.8
Lycatab PGS/ Corn starch	40	40	40	40	40	40	30	25	25	40
Klucel LF	8	8	8	12	12	10	12	12	12	8
HPMC	4	4	4	4	4	4	4	4	4	4
Avice.8l	35	44	63	55	46	64	55	32	45	55
Ca CMC	12	12	8	2	8	8	25	25	25	8
Mg.stearate	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Total (mg)	**420**	**420**	**420**	**420**	**420**	**420**	**420**	**420**	**420**	**420**

Table.8. The evaluation results for flow properties of granules are described in the following table.

S.No	Formulations	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner's Ratio
1	F-1	0.596	0.785	24.07	1.31
2	F-2	0.581	0.714	18.60	1.22
3	F-3	0.654	0.802	18.45	1.22
4	F-4	0.694	0.834	16.67	1.2
5	F-5	0.480	0.625	23.07	1.30
6	F-6	0.519	0.732	29.09	1.443
7	F-7	0.583	0.745	21.74	1.277

8	**F-8**	**0.582**	**0.714**	**18.60**	**1.22**
9	F-9	0.510	0.641	20.40	1.25
10	F-10	0.500	0.735	32	1.470

Evaluation of granules

Inference:

A. F – 1, F – 5, F – 7 showed "Passable" flow properties
B. F-2, F-3, F-4, F-8, F-9 showed "Fair" flow properties
C. F-6, F – 10 showed very poor flow properties

Table.9. The evaluation results of in process properties of tablets are described in the following table.

S.No	Formulations	Thickness (mm)	Hardness (kg/cm^2)	Disintegration (Min)	Friability (%)	Assay (%)
1	F-1	3.62 ± 0.099	4.1 ± 0.03	3.16	0.153	96.4
2	F-2	3.62 ± 0.016	5.1 ± 0.03	3.02	0.106	97.3
3	F-3	3.46 ± 0.035	6.19 ± 0.22	8.5	0.377	94.1
4	F-4	3.46 ± 0.024	9.75 ± 0.51	14.55	0.24	98.5
5	F-5	3.48 ± 0.029	10.44 ± 0.49	11.5	0.17	97.4
6	F-6	3.47 ± 0.053	5.46 ± 0.32	11.2	0.28	98.3
7	F-7	3.47 ± 0.052	9.45 ± 0.59	12	0.23	92.4
8	**F-8**	**3.53 ± 0.022**	**8.12 ± 0.47**	**11**	**0.06**	**99.8**
9	F-9	3.55 ± 0.019	9.6 ± 0.35	5.5	0.06	98.5
10	F-10	3.55 ± 0.016	7.1 ± 0.27	2	0.167	98.2
11	**Innovator**	**3.50 ± 0.04**	**9.8 ± 0.14**	**11.17**	**0.15**	**98.8**

Evaluation of tablets

In-vitro dissolution release:

Comparative *In-vitro* Dissolution release profile for Reference and all formulations at 60 Minutes is given in the following table and Figures.

Table.10. 20 % of Drug Release (Voriconazole)

S.No	Time	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	Innovator
1	10	67.6	86.4	68.9	31.6	56.5	41.4	38.4	**67.4**	84.7	80	**40.9**
2	20	72.4	95.8	96	61.8	86.5	79.9	74.5	**94.5**	94.7	87.8	**73.7**
3	30	77.9	103.8	97.6	84.0	96.2	94.9	97.0	**98.9**	98.9	91.2	**89.6**
4	45	84.6	104.5	97.9	94.9	96.4	100.1	104.3	**99.7**	104.6	93.4	**96.2**
5	60	92.5	106.5	98.6	98.3	97.1	102.6	106.5	**99.9**	107.0	94.7	**98.6**

We selected **F - 8** as the best formulation as it showed total drug release within 30 min than all other formulations when compared to the reference product.

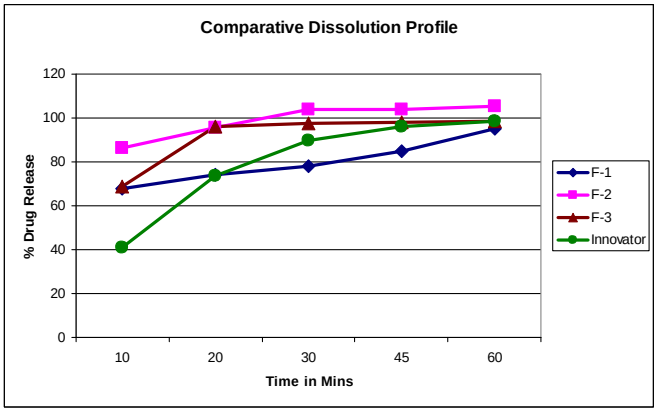


Fig : Comparative In-vitro Drug release of Trials F – 1, 2, 3 and Reference Drug

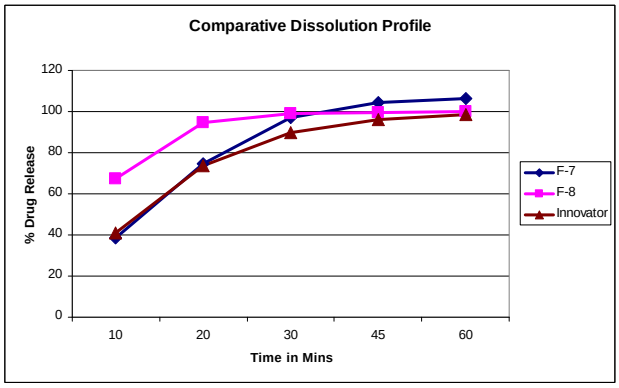


Fig: Comparative In-vitro Drug release of Trials F – 7, 8 and Reference Drug

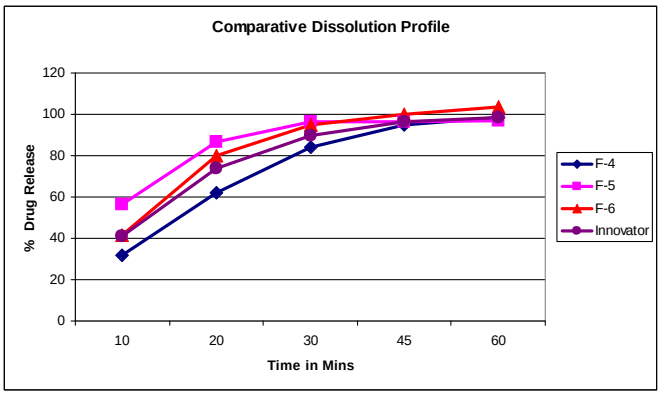


Fig: Comparative In-vitro Drug release of Trials F – 4, 5, 6 and Reference Drug

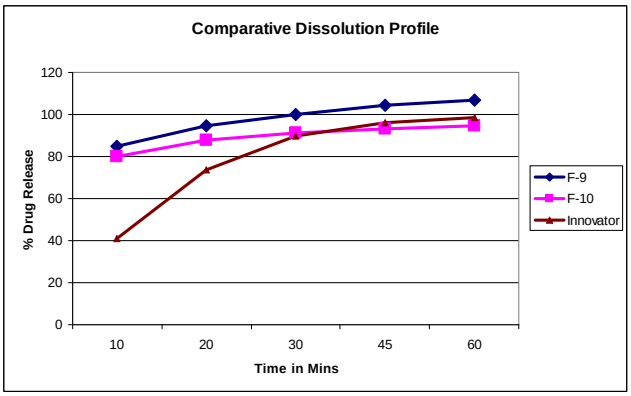


Fig: Comparative In-vitro Drug release of Trials F – 9, 10 and Reference Drug

Stability Data of Trial F – 08: Dissolution of trial F – 08 tablets were comparable with reference product.So, tablets of this batch were kept for stability studies. The results of stability studies are shown in the following table. After 3 months the physical parameters of the tablets were same. Water content and related substance are within limits. Tablets were passing the stability studies. The tablets were tested for average weight, thickness, hardness, friability, Disintegration, water content and RS at initial, 1 month and 3 months.

Table 11 : Stability Study data of Trial F – 08

S.No	Parameters	Conditions			
		Initial	$25^0C \pm 2^0C$	40 ± 2^0C & 75 ± 5% RH	
		0 Day	3 Months	1 Month	3 Month
1	Average Weight	260.2 ± 0.13	259.4 ± 0.2	261.4 ± 0.23	261.6 ± 0.3
2	Thickness	3.53 ± 0.02	3.51 ± 0.04	3.52 ± 0.06	3.48 ± 0.02
3	Hardness	8.12 ± 0.47	7.8 ± 0.24	8.1 ± 0.36	7.7 ± 0.45
4	Friability	0.06	0.3	0.17	0.21
5	Disintegration	11	10	11	9
6	Assay	99.8	101.9	97.7	94.3

4. Conclusion

Based on Literature survey and Compatibility Test excipients like Microcrystalline Cellulose (pH 101), PGS, Hydroxypropyl cellulose, Carboxy Methyl Cellulose, Magnesium stearate were used. In this present study, the tablets were prepared by using wet granulation technique. In order to optimize the product, different formulations were developed. All the formulations were evaluated for physical characteristics, Disintegration, *in-vitro* Dissolution and Stability studies. Based on the results of the above-

mentioned tests Trial F – 08 was selected as the best formulation. Stability studies were performed for this batch for 1 and 3 months under accelerated and long-term testing conditions. Finally, after the duration, the product was analyzed for physical appearance, Hardness, Thickness, Friability, Loss on drying, disintegration, Assay and Related substance. The results obtained were found to be with in the specified limits. The bigger scale confirmatory batch is under 6 months Accelerated stability condition, based on the result, a pilot scale will be executed. After passing the above tests, the in-vivo studies (BA/BE Studies) will be executed to correlate the bioequivalence of best formulation (Trial F – 08) with the reference drug.

5. References

[1] Akira Matsumori. Efficacy and safety of oral candesartan cilexetil in patients with congestive heart failure. Eur J Heart Fail (2003) 5 (5): 669-677.

[2] Alaa A. Al Omaria, Mahmoud M. Al Omarib, Adnan A. Badwanb, Khaldoun A. Al-Sou'oda. Effect of cyclodextrins on the solubility and stability of candesartan cilexetil in solution and solid state. Journal of Pharmaceutical and Biomedical Analysis (2010) 3, 124-135.

[3] Amy M Franks, Catherine E O'Brien, Cindy D Stowe, Thomas G Wells MD. Candesartan Cilexetil effectively reduces blood pressure in hypertensive children. The Annals of Pharmacotherapy 2008 July: Vol. 42, No. 10, 1388-1395.

[4] Erland Erdmann, Michael George, Bernhard Voet, Doris Kolb. The safety and tolerability of candesartan cilexetil in CHF. Journal of Renin-Angiotensin-Aldosterone System March 2000. Vol. 1, No. 1, Suppl 31-36.

[5] Graham A. MacGregor; J. Reuven Viskoper, Tarek F.T. Antonios, Feng J. He. Efficacy of Candesartan cilexetil alone or in combination with amlodipine and hydrochlorothiazide in moderate-to-severe hypertension. Hypertension 2000, 36:454.

[6] Toblli J E , Stella I , Mazza O N , Ferder L, Inserra F . Candesartan cilexetil protects cavernous tissue in spontaneously hypertensive rats. International Journal of Impotence Research (2004) 16, 305–312.

[7] Jean-Philippe Baguet, Gilles Barone-Rochette, Yannick Neuder. Candesartan cilexetil in the treatment of chronic heart failure. Volume 2009:5 Pages 257 – 264.

[8] Baguet JP, Asmar R, Valensi P, Nisse-Durgeat S, Mallion JM. Effects of candesartan cilexetil on carotid remodeling in hypertensive diabetic patients: the MITEC study. Volno**.** 2009:5 Pages 175 – 183.

[9] Homma K , Hayashi K , Kanda T , Yoshioka K , Takamatsu I , Tatematsu S , Kumagai H , Wakino S, Saruta T . Beneficial action of candesartan cilexetil plus amlodipine or ACE inhibitors in chronic nondiabetic renal disease. Journal of Human Hypertension (2004) 18, 879–884.

[10] Marc Pfister, Franziska Schaedeli, Felix J Frey, Dominik E Uehlinger. Pharmacokinetics and haemodynamics of candesartan cilexetil in hypertensive patients on regular haemodialysis. Br J Clin Pharmacol. 1999 June, 47(6): 645–651.

[11] McClellan K.J, Goa K.L. Candesartan cilexetil: a review of its use in essential hypertension. Volume 56, November 1998 (5) 847-869(23)

[12] See S, Stirling AL. Candesartan cilexetil: an angiotensin II-receptor blocker. American Journal of Health-System Pharmacy, Vol 57, Issue 8, 739-746.

[13] Stoukides CA, McVoy HJ, Kaul AF. Candesartan cilexetil: an angiotensin II receptor blocker. Ann Pharmacother. 1999, Dec 33(12):1287-98.

[14] Vijaykumar Nekkanti, Pradeep Karatgi, Mahendra Joshi, Raviraj Pillai. Developing nanoparticle formulations of poorly soluble drugs. Pharmaceutical technology europe, nov 1, 2008.

[15] Fang Gao, Zhiwen Zhang, Huihui Bu, Yan Huang, Zhiwei Gao, Jianan Shen, Chunjie Zhao, Yaping Li. Nanoemulsion improves the oral absorption of candesartan cilexetil in rats: Performance and mechanism. Journal of Controlled Release 2010 (2) 347-369(23).

[16] 16. Patel U, Patel K, Shah D, Shah R. A review on immediate release drug delivery system. International journal of pharmaceutical research and bio-science. 2012; 1(5): 37-66.

[17] 17. Bhattacharjee A. Formulation and evaluation of immediate release tablets of bromocriptine mesylate by direct compression method. Indo american journal of pharmaceutical research. 2013; 3(3): 2841 – 2845.

[18] 18. Alton ME. Pharmaceutics the science of dosage form design. Second edition. churchilllivngstone; 2002.

[19] 19. Gowtham M, Vasanti S, Rohan RD, Ashwath N, Paridhavi M. Formulation and evaluation of immediate release folic acid tablets. Scholars Research Library. 2011; 3 (6): 157-162.

[20] 20. Pathak N, Kumar A, Methkar V, Pant P, Rao RT. Formulation and optimization of immediate release tablet of an antialcoholic drug by dry granulation method. International Journal of comprehensive pharmacy. 2011; 2(3): 1-4.

[21] 21. Shilpa SK, Kumar AM, Garigeyi P. Formulation and optimization of clopidogrel bisulfate immediate release tablet. International journal of

pharmaceutical, chemical and biological sciences. 2012; 2(1): 38-51.

[22] 22. British Pharmacopoeia: British Pharmacopoeia Commission Office. London; 2013.

[23] 23. Tiwari AK, Shah H, Rajpoot A, Singhal M. Formulation and in-vitro evaluation of immediate release tablets of drotaverine HCl. Journal of chemical and pharmaceutical research. 2011; 3(4): 333-341.

[24] 24. Hosokawa R: Japanese Pharmacopoeia. The Minister of Health, Labour and Welfare Ministerial Notification No. 65 16th edition; 2011.

[25] 25. USP 30-NF 25. The United States Pharmacopoeial Convention. The official compendia ofstandards 2007; Copyright 2006.

[26] 26. Indian Pharmacopoeia: Volume 2: The Indian Pharmacopoeia Commission Ghaziabad 2007.

[27] 27. Rai VK, Pathak N, Bhaskar R, Nandi BC, Dey S, Tyagi LK. Optimization of immediate release tablet of raloxifene hydrochloride by wet granulation method. International journal of pharmaceutical sciences and drug research. 2009; 1(1), 51 – 54.

[28] 28. Inamdar M, Abhang P. Formulation and evaluation of immediate release tablets of tramadol HCl using different superdisintegrants. International journal of advances in pharmaceutical research. 2012; 3 (11): 1240 – 1245.

[29] 29. Kim Huynh-Ba. Handbook of stability testing in pharmaceutical development regulations, methodologies, and Best Practices, Publisher-Springer Science Business Media, LLC, 233 Spring Street, New York, NY 10013, USA; July 2008.

[30] 30. World Health Organization, Stability testing of active pharmaceutical ingredients and finished pharmaceutical products, WHO Technical Report Series, No. 953; 2009. Annex 2.2-357.