FORMULATION AND OPTIMIZATION OF IMMEDIATE RELEASE TABLET OF AN ANTI HYPERTENSIVE DRUG BY DRY GRANULATION METHOD

*Sowmya C, Suryaprakash Reddy C, Haranath C, Madhukar B

Raghavendra Institute of Pharmaceutical Education and Research,

Anantapur, Andhra Pradesh, India – 515 721.

_____

Abstract

The present study is planned to develop Candesartan cilexetil into immediate release tablets. Generally dry granulation is followed for the drugs that are sensitive to the moisture .Here the dry granulation was developed as a cost effective step towards the manufacturing compared to the wet granulation. The stability of the drug was also assured in the dry granulation process due to the absence of the moisture. So wet granulation method was avoided. All the mentioned batches were done by dry granulation method by roller compaction. Granules were evaluated for tests such as bulk density, tapped density, compressibility index and Hauser's ratio and sieve analysis before compression. Tablets were tested for weight variation, thickness, hardness, friability and dissolution. In vitro dissolutions were performed and Difference factor (f_1) and similarity factor (f_2) values were calculated. Dissolution profile of Trail V was found to have high similarity with marketed (innovator) formulation. First order dissolution model was constructed.

Key words: Candesartan Cilexetil, Immediate release tablet, Dry granulation technique, Difference factor, Similarity factor.

_____

Introduction

Candesartan blocks the vasoconstrictor[1] and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is, therefore, independent of the pathways for angiotensin II synthesis. The present drug (API) is a class II molecule[2, 3]; it dissolves slowly in aqueous environment and permeates over intestinal membrane fastly. Candesartan Cilexetil, a prodrug[4], is hydrolyzed to candesartan during absorption from the gastrointestinal tract.

Direct compression[5] of powders requires materials exhibiting flowability and compressibility.Those parameters become more critical when the formulation contains large amounts of active substances with poor compressional properties. Spray-dried extracts

_____

Author for Correspondence:

Sowmya C,

Raghavendra Institute of Pharmaceutical Education and Research,

Saigram, KR Pally cross, Chiyyedu, Anantapur, Andhra Pradesh, India– 515721.

Email: drsowmyariper@rediffmail.com

(SDEs) from medicinal plants are very fine, light, and poorly compressible powders. Few studies have examined the use of dry granulation to enhance particle size and consequently to improve flowability and compressibility of such materials. Dry granulation can be achieved either by slugging using a tablet press or by roller compacter. Both of these processes are used for materials that ordinarily will not compresssing the more conventional wet granulation techniques and require precompression to increase density or exclude entrapped air due to porosity.[5]

The granulation parameters can affect the mechanical (compressional) properties of the granules, which subsequently can influence the tableting behavior and tablet characteristics[6]. The desired particle size distribution can be adjusted by milling and sieving[7].The granulation parameters can affect the mechanical (compressional) properties of the granules, which subsequently can influence the tabletting behavior and tablet characteristics. Therefore, the evaluation of granule properties plays an important role in the prediction of tablet characteristics. Immediate release oral dosage forms are most widely used drug delivery systems available. These products are designed to disintegrate in the stomach followed by their dissolution in the fluids of the gastrointestinal tract. In limited number of cases, an *in-vitro   in-vivo* correlation is established between the drug release and drug product absorption necessary for therapeutic effects. Disintegration test is a standardized test and is primarily used as a quality assurance tool to confirm complete disintegration of solid oral dosage forms within the prescribed time when placed in a liquid medium under the experimental conditions described in their respective official monographs[8]. The methods for the comparison of in vitro dissolution profiles can be classified into three groups: methods based on analysis of variance (ANOVA) [9, 10] model-dependent methods[11], and model-independent method[12, 13]. In this context, The discrimination of release profiles was compared with a marketed formulation using model-dependent and model-independent methods.

Table 1: Formula used in the different formulations

Ingredients (mg/tab)	F1	F2	F3	F4	F5
Intragranular Ingredients					
Candesartan cilexetil	32	32	32	32	32
Lacto press Spray Dried 250	242.5	239	239	235	237.5
Corn starch	55	25	--	55	46
Starch1500	--	--	55	--	--
Carmellose calcium	8.00	12	--	12.0	20.0
Extragranular ingredients					
Avicel PH-112	8.5	8.0	4.0	6.0	6.0
Carmellose calcium	--	--	4.0	6.0	4.0
Magnesium stearate	4.0	4.0	4.0	4.0	4.0
Starch1500	--	30	12	--	--
Colloidal silica	--	--	--	--	--
Total	**350**	**350**	**350**	**350**	**350**

Materials and methods

Candesartan Cilexetil (Zydus Cadilla), Lactopress Spray Dried 250 (DMV-Fonterra), Corn starch (Roquette Freres), Carmellose calcium (Maple Biotech), Magnesium stearate (Ferro corporarion), Colloidal silica (Evonik Industries GMBH).

Solubility studies of Candesartan cilexetil

Maximal solubility of Candesartan cilexetil in different media (0.7% polysorbate in pH6.5 Phosphate Buffer, 0.7% polysorbate in pH4.5 Acetate Buffer, 0.7% polysorbate in 0.001N HCl, 0.7% polysorbate in 0.1N HCl) was studied. Excess amount of Candesartan cilexetil was taken in 50 mL of above medium and dissolved by triplicate sonication. The maximal solubility of Candesartan cilexetil in each medium was determined at different time intervals (0, 15, 60, 120min) after filtering the content using HPLC method.

Preparation of Candesartan cilexetil tablets

Immediate release tablet of Candesartan cilexetil were prepared by adopting dry granulation technique. Accurately weighed quantities of pre-sieved drug and intragranular materials (Candesartan cilexetil, Lactopress® Spray Dried 250, Corn starch, Carmellose calcium) were mixed & slugs were prepared, and then passed through multimill screen (1.5"). The granules were sieved using #20 sieves.

The final granules were blended with extragranular materials (Magnesium stearate, Colloidal silica) and compressed using 9.5 mm round flat standard concave Punches on Tablet Compression Machine (16 Stations, D Tooling), Cadmach, INDIA.. Three batches of tablets were prepared for each formulation. Composition of prepared Candesartan cilexetil immediate release tablets are presented in table 1 Physical properties of granules of different formulations were determined in table 2.

Evaluation of tablet properties

The formulated tablets were evaluated for uniformity of weight, thickness, hardness, friability and disintegration time.

Weight variation test

The variation of the weight of individual tablet is a valid indication of the drug content. Weight variation studies of 20 tablets were done and resulting deviations were determined and the results were shown in the table 3.

Thickness measurement

It is carried out on 20 tablets by measuring thickness using vernier calipers. Mean and standard deviation were determined and the results were shown in table 3.

Hardness determination

20 tablets were taken randomly and hardness was measured using Hardness tester (Electrolab India Ltd). The mean and standard deviation of 20 tablets of each formulation is shown in table 3.

Friability test

Friability was determined on 20 tablets. Tablet samples were weighed accurately and placed in fribilator (Electrolab India Ltd). After 100 rotations (4 min at 25 rpm) loose dust was removed from the tablets. Finally tablets were weighed. The loss in weight indicates the ability of the tablets to withstand the wear. The percentage friability was determined by using

following formula and the result was shown in table 3.

$$\% \, friability = 100 \, X \, \frac{initial \, wt \, of \, tablet - final \, wt \, of \, tablet}{initial \, wt \, of \, tab}$$

Disintegration test

Disintegration time was determined to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract. The tablets were examined using the USP- XXIV disintegration apparatus (Electrolab India). Six tablets were tested for each batch. The disintegration time of tablets was compared to 15 minutes which is accepted as the general tablet disintegration time for the uncoated immediate release tablets. The results of the disintegration time of the various formulations were shown in table 3.

In-vitro release studies

In-vitro release study of Candesartan Cilexetil was carried out using USP Type II dissolution apparatus (Paddle type, model TDT-08L, Electrolab, India) at 37±1°C and 50 rpm using 900 mL with 0.7% polysorbate in pH 6.5 Phosphate Buffer. Aliquots were withdrawn at predetermined time intervals and were replenished immediately with the same volume of fresh dissolution medium. Aliquots, following suitable dilutions, were assayed by HPLC (Shimadzu, Japan) at 227 nm. The drug release profiles of the various formulations were shown in table 4.

Drug content study

5 tablets or blend equivalent to 5 tablets were weighed and transferred into 100 ml volumetric flask. To this 70 ml of diluent (Phosphate buffer and Acetonitrile in the ratio of 30:70) was added and sonicated to dissolve

with intermittent shaking. Further dilute 5 mL of the above solution to 100mL. The solution was mixed well and filtered through 0.45 µm nylon filter. After injecting the blank, standard then the sample was injected and the drug content was calculated using HPLC at 227 nm. The drug content of the various formulations was shown in table 3.

Model-independent methods- Determination of dissolution data equivalence

For the determination of dissolution data equivalence, FDA guidance documents recommend approaches such as the model-independent approach based on the calculation of difference factor (*f1*) and similarity (*f2*) factors, which is currently applied. From a statistical point of view, this method seems to be less discriminating than other methods, such as ANOVA and model-dependent methods. According to the FDA guidance, *f1* values of 0–15 and *f2* values of 50–100 ensure sameness or equivalence of the two dissolution profiles. In both equations, *R* and *T* represent the dissolution measurements at *P* time points of the reference and test, respectively. Difference factor (*f1*) and similarity (*f2*) factors were calculated for every formulation and they were shown in table 4

$$f_1 = \{[\textstyle\sum_{i=1}^{p} |R - T|]/[\textstyle\sum_{i=1}^{p} R]\} \, 100$$

$$f_2 = 50 \, \log\{[1 + \tfrac{1}{p} \textstyle\sum_{i=1}^{p}(R - T)^2]^{-1/2} \, 100\}$$

Model-dependent methods

Drug release kinetics was analyzed by first-order kinetic model, which was applied considering the amounts of drug released from 0 to 60 min. The following plot was made: log cumulative % drug remaining versus time (first-order kinetic model) and it was shown in

the figure 02. K_1 (First order release constant) calculated for all the formulations as shown in the table 5.

Results and discussion

Flow properties of the drug are important in optimizing the method of granulation for the drug product. Therefore, the flow of drug was analyzed before the selection of granulation technique. Hausner's ratio (≤1.35), compressibility index (≤30) and angle of repose (≤45) indicates poor flowability of drug candidate, the dry granulation technique, was selected to improve the flow ability of powder mixture.

Experiments with solubility of Candesartan Cilexetil in various medium revealed that Candesartan Cilexetil is more soluble in 0.7% polysorabte in 0.05M phosphate buffer pH 6.5. Hence, it was selected as ideal dissolution medium, to study *in-vitro* release profile of Candesartan Cilexetil.This medium is the FDA recommended for the dissolution of the Candesarten Cilexetil tablets.

The optimization of the formula was done by varying the the concentrations of the disintegrants like corn starch, Starch 1500, Carmellose calcium both intra granularly and extra granularly. MCC PH-112 was changed only extra granularly.

In the first formulaion all the physical parameters were comparable to that of the innovator except the disintegration time. In the second formulation corn starch was used 7% intra granularly and 8.5% (starch 1500) was used extra granularly. The disintegration time found to reduce substantially compared to the reference product. In the third formulation disntegrant(Starch 1500) was used only intra granularly and only 1.2% Carmellose calcium was used extra granularly.The DT was found to increase by only 1 minute.There were no changes in DT with Starch1500.In the next formulations only corn starch and carmellose calcium were used

In the fourth formulation 15% of the corn starch, 3.5% of Carmellose calcium was used intra granularly as disintegrant and 1.8% (Carmellose calcium) was used extra granularly.In this formulation the DT was found to slighly match with that of the innovators DT (10-11 min).In the fifth formulation the extra granular disintegrants were slightly reduced and the DT was found to be matching with that of the innovator's product.By comparing the dissolution profiles fourth and the fifth formulations were comparable to that of the innovators product. The fifth formulation was found to be matching more in terms of the similarity factor.

First order dissolution model was constructed and t_{50} and t_{90} were calculated.

Conclusion

Candesartan Cilexetil immediate release tablets were prepared by dry granulation technique. In order to obtain the best, Optimized product five different formulations were developed. Different disintegrants and their concentration were taken as the major variables. An optimized product has been formulated by varying the above variables and determining their effect on physical/ mechanical properties of the final product.

Lower compressibility and poor flow of drug candidate was overcome by dry granulation (slugging). Release of the drug from the tablet was found to follow the first order kinetics, Similarity factor was calculated and the Trail V was found to match with the innovator product. t_{50}, t_{90} values (time taken to reach 50% and 90% release simultaneously) were calculated and these values of the optimized formulation were found to match with the innovators product.

Table 01: Flow properties (Pre compression parameters) of the different formulations-Mean and standard deviations were included

Properties	Trail I	Trail II	Trail III	Trail IV	Trail V
Angle of repose	28.1±0.04	26.6±0.06	28.4±0.02	26.0±0.03	23.8±0.09
Bulk density (gm/mL)	0.54±0.02	0.55±0.08	0.53±0.02	0.54±0.03	0.55±0.03
Tapped density (gm/mL)	0.68±0.04	0.69±0.03	0.68±0.03	0.69±0.02	0.69±0.02
Compressibility Index	27.0±1.06	26.1±1.07	25.77±1.37	21.65±1.25	23.52±1.52
Hausners Ratio	1.36±0.09	1.30±0.18	1.35±0.24	1.27±0.22	1.33±0.19

Table 02: Physical Chemical parameters of the tablets of the various formulations-Mean and standard deviations were included

Physical parameter	Trail I	Trail II	Trail III	Trail IV	Trail V
Hardness (N)	59±3.40	62±2.56	64±4.5	65±1.77	67±2.33
Thickness (mm)	4.25±0.13	4.2±0.76	4.26±0.35	4.22±0.36	4.2- 0.15
DT (min)	5-6	7-8	8-9	10-11	10-12
Friability (%w/w)	0.48	0.02	0.12	0.10	0.22
Weight (mg)	351.23±3.1	348.01±1.3	355±2.11	352.12±1.5	352±1.55
Drug content(%w/w)	98.17±3.55	97.1±1.29	101.7±1.4	98.7±1.09	98.9±0.34

Table 03: In vitro release studies of the various formulations

	% Mean cumulative drug release ± S.D.					
Time	Reference	Trail I	Trail II	Trail III	Trail IV	Trail V
10	27.1± 0.65	18.3±0.45	45.5±0.48	44.8±0.37	29.9±0.59	28±0.76
20	63.6± 0.77	41.5±1.88	70.3±0.97	82.1±1.33	59.5±0.66	63.1±0.56
30	88.8±1.34	61.9±1.67	92.7±1.78	88.5±1.65	79.6±1.29	82.8±1.77
45	99.9± 2.33	79.5±2.56	93.4±1.88	94.2±2.21	87.7±2.5	91.3±2.47
60	98.4±3.02	89.7±3.77	95.2±3.89	96.4±3.78	92.0±3.01	98.4±3.02

Table 04: f_1 and f_2 Values for Each Comparison

Formulation	f_1	f_2	Dissolution profile
Trail I	22.75	36.5	Dissimilar
Trail II	11.41	46.60	Dissimilar
Trail III	9.95	51.36	Similar
Trail IV	8.89	56.54	Similar
Trail V	3.92	68.31	Similar

Table 05: Release characteristics

Trail	First order Equation	First order R^2	K_1(min-1)	t_{50} (min)	t_{90} (min)
I	y = -0.0168x + 2.0606	0.9887	0.038	24.5	N.A.
II	y = -0.0244x + 1.9012	0.9549	0.056	11.5	28.5
III	y = -0.0232x + 1.9011	0.8915	0.053	12.2	32.5
IV	y = -0.0192x + 1.9862	0.9799	0.0442	16.5	48
V	y = -0.0294x + 2.1086	0.9731	0.0677	16.8	38
Reference	y = -0.0359x + 2.1203	0.9519	0.0826	17.2	34

t_{50} (min): Time taken to reach 50% cumulative drug release

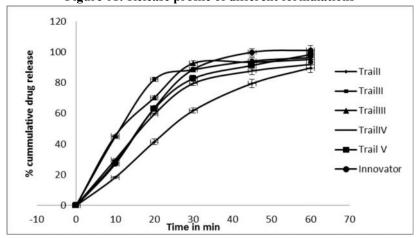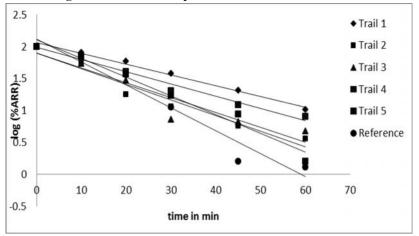t_{90} (min): Time taken to reach 90% cumulative drug release

N.A.: Not applicable

Figure 01: Release profile of different formulations

Figure 02: First-order plots for different formulations.

ARR – Amount remaining to be released

References

1. H.P. Rang, M.M. Dale, J.M. Ritter, R.J. Flower; *Rang and Dales Pharmacology*. Sixth Edition; 305-310.

2. Gilbert S. Banker Christopher T. Rhodes; fourth edition, Marcel Dekker,Inc, New York ; pp:55-57.

3. Vijaykumar N, Venkateswarlu V and Raviraj P Research Journal of Pharmaceutical, Biological and Chemical Sciences October – December 2010 RJPBCS 1(4) Page No. 952-63.

4. Description of Candesartan cilexetil; http://www.drugbank.ca/drugs/DB00796

5. Herbert.A. Liebermen, Leon Lachman, Joseph B.Schwartz, *Pharmaceutical dosage forms tablets,* Vol3, Second edition, Marcel Dekker,Inc, New York ,pp: 195-245.

6. Bultmann J M; Multiple compaction of microcrystalline cellulose in a roller compactor. *Eur J Pharm Biopharm*. 2002; 54:59-64.

7. Freitag F, Kleinebude P; How do roll compaction/dry granulation affect the tablet behavior of inorganic materials? Comparison of four magnesium carbonates. *Eur J Pharm Sci*. 200319:281-289.

8. United States Pharmacopeia 30/National Formulary 25. 2008. The U.S. Pharmacopeial Convention, Inc. Rockville, MD. (www.usp.org)

9. Mauger, J. W.; Chilko, D.; Howard, S. On the analysis of the dissolution data. *Drug Dev. Ind. Pharm*. 1986, *12*,969–992.

10. Polli, J. E.; Rekhi, G. S.; Augsburger, L. L.; Shah, V. P.Methods to compare dissolution profiles and arationale for wide dissolution specifications for metoprolol tartrate tablets. *J. Pharm. Sci*. 1997, *86*,690–700.

11. Sathe, P. M.; Tsong, Y.; Shah, V. P. In vitro dissolutionprofile comparison: statistics and analysis, model dependent approach. *Pharm. Res*. 1996, *13*,1799–1803.

12. Podczeck, F. Comparison of in vitro dissolution profiles by calculating mean dissolution time (MDT) or mean residence time (MRT). *Int. J. Pharm*. 1993, *97*, 93–100.

13. Moore, J. W.; Flanner, H. H. Mathematical comparison of dissolution profiles. *Pharm. Technol*. 1996, *6*, 64–74.