IJPSR (2017), Volume 8, Issue 11 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 15 December, 2016; received in revised form, 21 July, 2017; accepted, 27 October, 2017; published 01 November, 2017

SOLID DISPERSION OF ORAL CANDESARTAN CILEXETIL TABLETS FOR HYPERTENSION: DEVELOPMENT AND CHARACTERISATION

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Keywords:

Solid dispersion, Candesartan cilexetil, ICH guidelines, Oral Tablets, Solubility

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ABSTRACT: The main aim of this study was to prepare solid dispersion of Candesartan cilexetil so as to improve its solubility and dissolution characteristics in order to enhance its oral bioavailability. Solid dispersion was formed by fusion method. 9 formulations (F1-F9) were prepared using different carriers *i.e.* Sorbitol, Polyethylene Glycol (PEG 6000) and Poloxamer 407 at different ratios of 1:1, 1:3, 1:5 each. Out of 9 formulations, F3, F5 and F9 formulation compositions were selected on the basis of solubility, % yield, drug content, *in-vitro* dissolution studies. F3, F5 and F9 formulations were further formulated in 3 batches (A, B, C) into conventional dosage forms (tablet) with ingredients such as lactose, SSG, MCC, magnesium sulphate, and talc. On the basis of physical and chemical evaluation (Disintegration and dissolution studies), F9 was considered as the optimized formulation. The Optimized formulation, F9 *i.e.* Batch C was further compared with the Marketed formulation (Atacand, 4 mg) and stability studies were performed according to ICH guidelines. The optimized formulation of solid dispersion of Candesartan cilexetil (F9) has showed tremendous solubility, dissolution as well as other characteristic and can be used for hypertension and explore, further.

INTRODUCTION: "Solid dispersion" has become an established solubilisation technique for poorly water soluble drugs in order to enhance the dissolution and oral bioavailability. Although there are various techniques such as particle size reduction, micronization, physical modifications, complexation, solubilisation, co solvency *etc*. which can enhance solubility and dissolution rate of insoluble drugs but these techniques have some practical limitations, solid dispersion technique overcome these practical limitations [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.8(11).4795-02

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

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.8 (11).4795-02

Solid dispersion though have numerous advantages, despite the advantages offered by the solid dispersions, the marketed products based on this technology are few [2]. The term "Solid dispersion" is based on the concept that the drug is dispersed in an inert water-soluble carrier at solid state. By preparing solid dispersion, it is possible to provide better dispersability and wettability to the drug by carrier material.

Carriers which are soluble and dissolve in water at a faster rate are widely used in pharmaceutical industries. The increase in dissolution rate of the drug may be due to the increase in wettability, hydrophilic nature of the carrier and due to reduction in particle size [3]. Fusion method has been used in order to prepare solid dispersion of active pharmaceutical ingredient by incorporating different carriers.

So, several water soluble carriers such as methyl cellulose, urea, lactose, polyvinyl pyrrolidone and polyethylene glycols and poloxamers are used as carriers for solid dispersion [4].

Candesartan is an angiotensin II receptor antagonist mainly used in the treatment of hypertension. Candesartan is classified under class II according to Biopharmaceutical classification system *i.e.* the drug shows low aqueous solubility and high permeability. Hence, the rationale of selecting the drug was to attain adequate concentration on improving the drug dissolution characteristic when administered as a tablet for better control of hypertension. Therefore, the objective of this study was to improve the dissolution characteristics of Candesartan cilexetil tablets in order to enhance its solubility and oral bioavailability using Solid dispersion technique *via* fusion method.

MATERIALS AND METHODS: Candesartan tablets were purchased from SMILEX Laboratories Pvt. Ltd., India and other raw materials used were of standard analytical grade. 9 Formulations of solid dispersion were prepared. Solid dispersion formulations (F1 - F9) containing drug with different ratios of carriers *i.e.* First generation carrier Sorbitol, Second generation carrier PEG 6000, Third generation carrier Poloxamer 407 were prepared using fusion method [5]. The ratios of drug and carrier were 1:1, 1:3, 1:5 as shown in **Table 1**. Evaluation of the solid dispersion formed was done by performing solubility studies [6, 7], percentage yield (% yield) [8], drug content [9, 10] as well as *in-viitro* Dissolution studies [11]. Optimizations of SD formulations were done through X-ray Diffraction analysis and Differential Scanning Colorimetry (DSC).

TABLE 1: DRUG AND CARRIER RATIO USED IN SOLID DISPERSION

Formulation code	Formulation	Drug: carrier	Method used
F1	Drug + Sorbitol	1:1	
F2	Drug + Sorbitol	1:3	Fusion method
F3	Drug + Sorbitol	1:5	
F4	Drug + PEG 6000	1:1	
F5	Drug + PEG 6000	1:3	Fusion method
F6	Drug + PEG 6000	1:5	
F7	Drug + Poloxamer 407	1:1	
F8	Drug + Poloxamer 407	1:3	Fusion method
F9	Drug + Poloxamer 407	1:5	

Solid dispersions Formulations (F3, F5 and F9) with best outcome result of *in-vitro* dissolution were formulated into conventional dosage form. Tablets were prepared by direct compression method [8]. All the ingredients were accurately weighed and screened through sieve no. 40. The mixture is compressed using 8 mm flat face punch on eight stages rotary tablet compress machine. All tablets contains Lactose as tablet filler and binder, SSG as disintegrant and dissolution aid, MCC as dispersing and stabilizing agent and Magnesium stearate as lubricant. Formulation chart is mention in the **Table 2**.

TABLE 2: LIST OF INGREDIENTS USED IN FORMULA

Ingredients	Quantity (mg)	Drug + Sorbitol (1:5) (Batch A)	Drug + PEG 6000 (1:3) (Batch B)	Drug + Poloxamer 407 (1:5) (Batch C)
Candesartan cilexetil	4	4:20	4:12	4:20
Lactose	115	95	103	95
SSG	20.5	20.5	20.5	20.5
MCC	10	10	10	10
Magnesium Stearate	0.40	0.40	0.40	0.40
Talc	0.10	0.10	0.10	0.10
Total	150	150	150	150

SSG: Sodium Starch Glycolate; MCC: Microcrystalline Cellulose.

The powder blend prepared for tablets were characterized with respect to Angle of repose, Bulk density, Tapped density, Hausner's ratio and Carr's index. Micromeritics properties of all the prepared batches *i.e.* Batch A, Batch B and Batch C were evaluated before tablet compression by the same

procedure used to determine the flow property of pure drug. The general appearance of a tablet includes shape, size, colour, surface texture *etc*. All the studies were performed in triplicate. Thickness was measured with the help of Vernier Callipers. All the studies were performed in triplicate [12]. Tablet hardness can be determined by using Monsanto hardness testers or Pfizer testers. Hardness of 10 tablets was determined and the average hardness was calculated [13]. The instrument used for this test is known as "friabilator". 20 tablets were weighed accurately before and after introducing them into the friabilator and subjected to 100 revolutions [12]. Twenty (20) tablets were selected at random and weighed individually using digital weighing balance. The average weight of one tablet was determined from the collective weight. Not more than two of the individual weight deviates from the average weight by more than percentage shown in the table and not by more than twice that percentage [14].

It was done through disintegration test as well as *in-vitro* dissolution studies. Disintegration test was carried out on 6 tablets using the disintegration test apparatus. Distilled water at 37.5 °C was used as a disintegration media and the time taken for the complete disintegration of the tablet was measured in seconds [15]. The *in-vitro* release study of Candesartan cilexetil tablets was done by using USP type II dissolution apparatus with the rotation speed of 50 rpm using Phosphate buffer pH 6.8 as dissolution medium maintained at a temperature 37 ± 0.5 °C. Samples were withdrawn at specific time intervals and filtered through Whatman filter paper, diluted suitably and analyzed at 255 nm for cumulative drug release using UV spectro-photometer [16, 19 - 21].

The quality and physicochemical equivalence of marketed brand of Candesartan cilexetil and optimized tablet of Candesartan cilexetil were accessed. The assessment included the evaluation of uniformity in weight, friability, hardness, disintegration and dissolution tests as well as chemical assay of the tablets. All the studies were performed in triplicate.

The stability study of optimized formulation was performed as per ICH guidelines. Tablets were evaluated for any statistical difference in their uniformity of weight, hardness, friability, disintegration and dissolution tests as well as chemical assay [17 - 21]. All the studies were performed in triplicate. The results of stability studies were plotted and analyzed on Sigma Plot 10.0 software by using pharmacological tool.

RESULTS: After preparation of solid dispersion, various evaluation studies were conducted and concluded in **Table 3**, **4** respectively. The results showed that the formulation prepared using Poloxamer 407 showed higher percentage yield *i.e.* 93.86 ± 0.66 than the other formulations prepared using polymers *i.e.* Sorbitol and PEG 6000. All the solid dispersions showed presence of high drug content and low standard deviation values. The results showed that the Formulation, F9 prepared using Poloxamer 407 showed higher drug content value *i.e.* 99.72 ± 1.24. The formulation F3, F5 and F9 displayed higher dissolution rate among all formulations. The solid dispersion of pure drug prepared with Poloxamer 407 revealed a reduction in peak intensity when compared to the XRD of plain drug as shown in **Fig. 1**.

The solid dispersion formulation of Poloxamer (2 mg) was sealed in aluminium pan and heated at a constant rate of 40 - 300 °C. The endothermic peak of solid dispersion was obtained at 57.66 °C ± 0.15. (Reported value 51.85 - 61.94 °C). The endothermic scan of solid dispersion shows less intense peak at 51.85 °C with marked decrease in sharpness, intensity and broadness as shown in **Fig. 2**.

TABLE 3: SOLUBILITY PERCENTAGE (%), YIELD PERCENTAGE (%), PERCENT (%) DRUG CONTENT PROFILE OF SOLID DISPERSION FORMULATIONS

S. no.	Formulation code	Solubility (mg/ml)	% Yield	% Drug content
1	F1	55.34 ± 1.12	79.52 ± 0.78	91.61 ± 1.13
2	F2	63.78 ± 1.24	83.58 ± 0.67	92.14 ± 1.24
3	F3	80.89 ± 1.35	88.97 ± 0.89	94.12 ± 1.30
4	F4	60.56 ± 1.19	89.64 ± 0.94	96.32 ± 1.15
5	F5	83.45 ± 1.52	92.72 ± 0.56	93.56 ± 1.18
6	F6	73.12 ± 1.87	92.10 ± 0.92	97.18 ± 1.20
7	F7	65.20 ± 1.38	88.69 ± 0.65	98.50 ± 1.28

8	F8	74.65 ± 1.47	86.32 ± 0.34	95.65 ± 1.52
9	F9	88.67 ± 1.75	93.86 ± 0.66	99.72 ± 1.24

(Values are mean ± SD, n = 3)

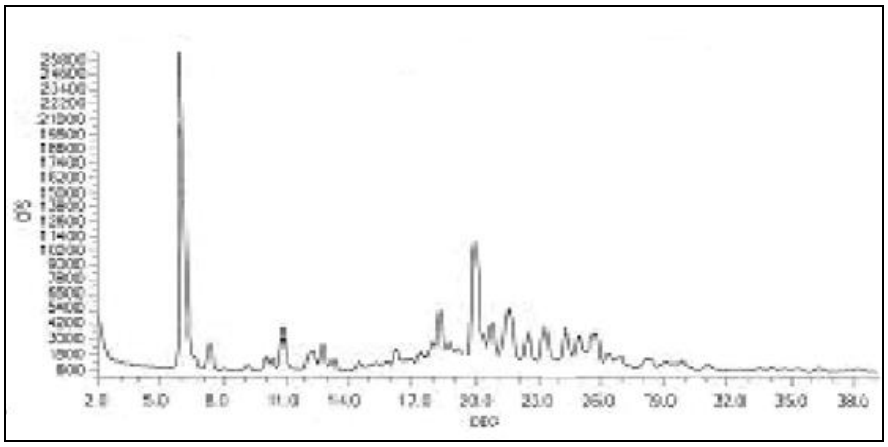

FIG. 1: X-RAY DIFFRACTROGRAM OF DRUG: POLOXAMER 407

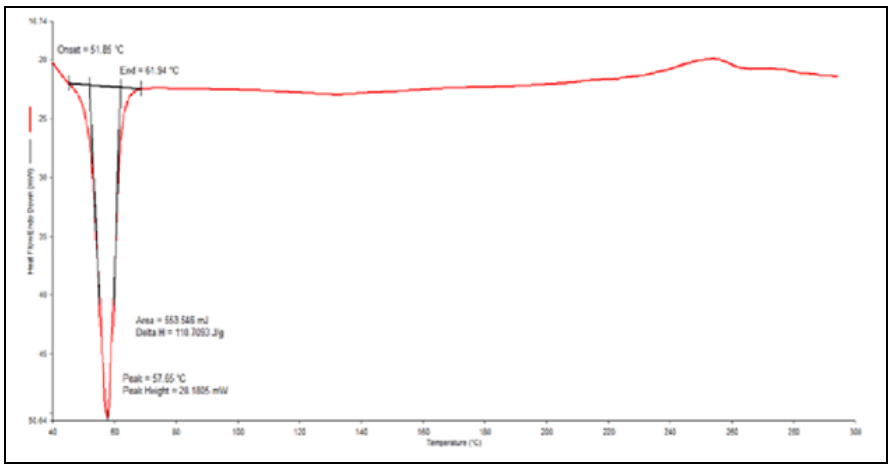

FIG. 2: DSC OF DRUG: POLOXAMER 407

Pure drug (Candesartan cilexetil) was formulated into solid dispersion tablets. The selected formulations F3, F5 and F9 were coded as Batch A, Batch B and Batch C. Tablets (150 mg) of Batch A, Batch B and Batch C were prepared by direct compression method. Finally, tablets were evaluated for various significant parameters to ensure the formation of a quality product. The powder blend prepared for tablets were characterized with respect to Angle of repose, Bulk density, Tapped density, Hausner's ratio and Carr's index. The result of pre-compression evaluation of powder blend for tablets was given in **Table 5**. The thickness was found in the range of 2.12 ± 0.36 to 2.40 ± 0.20 mm. The measured hardness of the tablets of each batch of all formulations was found in the range of 5.2 ± 0.52 to 6.2 ± 0.78 Kg/cm^2 and the results are shown in **Table 6**. The value of friability test ranges from 0.37 ± 0.12% to 0.52 ± 0.10% tabulated in **Table 6**.

Weight variation for the tablets conducted for each batch of all formulations was found to be within the range of 148.37 ± 1.65 to 149.42 ± 1.15 mg as shown in **Table 6**. The weight variation test for all formulations compiles within the limits of I.P. *i.e.* ± 5%. The disintegration time was found in the range of 4.46 ± 1.21 to 6.52 ± 1.32 min as tabulated in **Table 6**. The result indicates that the percentage of drug release was found to be 78.53 ± 1.45% to 88.16 ± 1.34% as shown in **Table 6**. Based on the above Tablet evaluation parameters, Batch C shows higher drug content and *in-vitro* release rate as compared to Batch A and Batch B.

Batch C was compared against a Marketed formulation *i.e.* Atacand (4 mg) tablets for different parameters. Various parameters were evaluated between optimized formulation (F9) and marketed formulation as tabulated in **Table 7**.

The stability studies were conducted on the selected formulations as per the ICH guidelines *i.e.* 40 ± 2 °C / 75 ± 5% RH. The stability studies were done at the intervals of 0, 15, 30, 60 and 90 days. The physical changes appeared in tablets were observed at certain time interval during 3 months of stability studies and results are summarized in **Table 8**. Moreover the chemical changes were also observed in terms of % drug release and drug content at above storage conditions and results are summarized in **Table 9**.

TABLE 4: DISSOLUTION RATE PROFILES OF CANDESARTAN CILEXETIL WITH SORBITOL, PEG 6000 AND POLOXAMER 407

	% Cumulative drug released									
		Sorbitol			PEG 6000			Poloxamer 407		
Time (in min)	Candesartan cilexetil	F1 (1:1)	F2 (1:3)	F3 (1:5)	F4 (1:1)	F5 (1:3)	F6 (1:5)	F7 (1:1)	F8 (1:3)	F9 (1:5)
5	12.17 ±0.45	18.62 ±054	30.41 ±0.68	42.16 ±0.34	28.42 ±0.72	46.92 ±0.42	48.40 ±0.84	26.25 ±0.20	48.45 ±0.54	58.57 ±0.65
10	15.21 ±0.64	20.82 ±0.34	46.14 ±0.42	56.42 ±0.24	34.91 ±0.35	58.51 ±0.18	54.04 ±0.53	34.42 ±0.73	54.64 ±0.23	61.24 ±0.56
20	19.34 ±0.15	30.58 ±0.65	54.59 ±0.35	69.70 ±0.20	39.07 ±0.69	64.34 ±0.20	56.54 ±0.42	40.21 ±0.28	63.12 ±0.18	74.52 ±0.50
30	22.23 ±0.34	34.89 ±0.23	64.36 ±0.54	77.25 ±0.44	42.33 ±0.45	69.67 ±0.27	62.23 ±0.78	55.33 ±0.40	72.43 ±0.25	78.43 ±0.64
45	24.43 ±0.51	39.12 ±0.54	68.91 ±0.45	83.17 ±0.18	44.11 ±0.19	74.98 ±0.38	68.13 ±0.63	74.12 ±0.55	79.16 ±0.40	85.31 ±0.19
60	27.32 ±0.43	43.16 ±0.19	72.42 ±0.25	85.11 ±0.45	45.05 ±0.52	82.04 ±0.65	74.16 ±0.44	76.36 ±0.21	86.18 ±0.30	89.21 ±0.23
90	28.12 ±0.24	48.14 ±0.32	79.70 ±0.43	88.42 ±0.42	52.38 ±0.54	89.62 ±0.35	82.32 ±0.33	79.41 ±0.38	94.21 ±0.56	96.32 ±0.34

(Values are mean ± SD, n = 3)

TABLE 5: MICROMERITIC PROPERTIES OF PREPARED FORMULATIONS

Formulations Batch	Angle of Repose (θ) ± S.D	Bulk Density (g/ml) ± S.D	Tapped Density (g/ml) ± S.D	Hausner's Ratio ± S.D	Carr's Index (%) ± S.D
Batch A (Drug + Sorbitol)	32.42 ± 1.33	0.45 ± 0.21	0.53 ± 0.42	1.24 ± 0.29	14.23 ± 0.32
Batch B (Drug + PEG6000)	33.15 ± 1.10	0.49 ± 0.42	0.52 ± 0.74	1.19 ± 0.44	15.44 ± 0.73
Batch C (Drug + Poloxamer 407)	31.82 ± 1.24	0.42 ± 0.82	0.51 ± 0.33	1.15 ± 0.92	12.15 ± 0.33

(Values are mean ± SD, n = 3)

TABLE 6: VARIOUS PARAMETERS EVALUATED FOR CANDESARTAN CILEXETIL TABLETS

Formulations	Hardness Kg/cm^2 ± S.D	Friability (%) ± S.D	Uniformity of weight ± S.D	Disintegration time (min) ± S.D	Drug content (mg) ± S.D	% drug release ± S.D (90 min)
Drug + Sorbitol (Batch A)	5.2 ± 0.52	0.37 ± 0.12	148.37 ± 1.65	4.46 ± 1.21	92.28 ± 1.21	78.53 ± 1.45
Drug + PEG 6000 (F5) (Batch B)	5.8 ± 0.46	0.52 ± 0.10	149.09 ± 1.35	6.52 ± 1.15	93.12 ± 1.13	82.12 ± 1.38
Drug + Poloxamer 407 (Batch C)	6.2 ± 0.78	0.41 ± 0.08	149.42 ± 1.15	5.22 ± 1.32	98.85 ± 1.15	88.16 ± 1.34

(Values are mean ± SD, n = 3)

TABLE 7: COMPARATIVE EVALUATION OF BATCH C AND MARKETED FORMULATION

Formulations	Hardness Kg/cm^2 ± S.D	Friability (%) ± S.D	Uniformity of weight ± S.D	Disintegration time (min) ± S.D	Drug content (mg) ± S.D	% drug release ± S.D (90 min)
Batch C (Drug + Poloxamer 407)	5.2±0.09	0.52±0.13	149.42±1.15	6.22±1.32	98.85 ± 1.35	88.16 ± 1.34
Marketed tablet	4.8±0.32	0.35±0.21	149.86±1.05	5.28±1.10	99.89 ± 1.15	86.34 ± 1.12

TABLE 8: PHYSICAL ACCELERATED STABILITY STUDY OF SELECTED BATCH C

Time (days)	Changes in physical characteristics at 40 ± 2 °C / 75 ± 5% RH				
	Colour	Thickness	Hardness	Weight variation	Friability
Initial	X	X	X	X	X
15	X	X	X	X	X
30	X	X	X	X	X
60	X	X	X	X	X
90	X	X	X	X	X

(X = No change)

TABLE 9: CHEMICAL ACCELERATED STABILITY STUDY OF SELECTED BATCH C

Time (days)	Changes in chemical characteristics at 40 ± 2 °C / 75 ± 5% RH Parameters	
	Drug content (mg / tablet)	*In-vitro* drug release
Initial	98.85 ± 1.05	88.16 ± 1.34
15	98.50 ± 1.12	87.45 ± 1.43
30	98.22 ± 1.32	87.20 ± 1.12
60	97.95 ± 1.22	86.54 ± 1.04
90	96.35 ± 1.15	85.25 ± 1.17

(Values are mean ± SD, n = 3)

DISCUSSION: Slower dissolution rate is the biggest problem associated with the oral dosage forms of poorly soluble drugs and often acts as a rate limiting factor for bioavailability of such drugs. Major problems associated with oral drugs are its low solubility in the body fluids which may result into poor bioavailability after oral administration. Candesartan cilexetil is an antihypertensive drug with low aqueous solubility, high permeability and shorter half-life. Hence, this drug is a good candidate for the solid dispersion development. Candesartan cilexetil is a drug of choice since it has higher affinity for angiotensin receptor and can be eliminated by both hepatic and renal excretion.

The rationale of this study was to improve solubility and dissolution rate of this drug thereby increase the frequency of administration and patient compliance by preparing solid dispersion. Preformulation studies were carried out to derive ideal properties of drug like Flow properties, Solubility profile, Partition behaviour and Drug-excipients compatibility studies. Solid dispersion using hydrophilic polymers as carrier substances were prepared to improve the dissolution rate of the selected model drug *via* fusion method.

Polymers used are listed as generally regarded as safe (GRAS) in US FDA list. Solid dispersion was prepared using three different carriers *i.e.* Sorbitol, PEG 6000, Poloxamer 407 in 1:1, 1:3, 1:5 ratios separately using Fusion method. 9 Formulations of solid dispersion were prepared using these carriers.

Solid dispersion Formulations were also characterized for physicochemical properties like Drug content, Solubility studies, Percentage yield and *In-vitro* dissolution studies. Solubility study of solid dispersion formulations ranges from 55.34 ± 1.12 to 88.67 ± 1.75. So1ubility studies revealed that solid dispersions prepared with Poloxamer 407 exhibited high solubility in phosphate buffer pH 6.8 as compared to other formulations prepared using other polymers.

The Percentage yield of solid dispersion Formulations ranges from 79.52 ± 0.78 to 93.86 ± 0.66 and Drug content ranges from 91.61 ± 1.13 to 99.72 ± 1.24. The Formulation F9 exhibited maximum percentage yield and drug content. The *In-vitro* dissolution study was carried out in Phosphate buffer pH 6.8 for 90 minutes. The release data obtained for Formulations F1 to F9. The % drug release of pure drug Candesartan cilexetil was found to be 28.12%. The plot of % drug released after 90 minutes was found to be 88.42% (F3), 82.32% (F5) and 96.32% (F9) for Sorbitol, PEG 6000 and Poloxamer 407. The solid dispersion Formulations (F3, F5 and F9) prepared with Sorbitol (1:3), PEG 6000 (1:3) and Poloxamer 407 (1:5) was found to yield better dissolution rate as compared to other formulations.

Out of 9 Formulations, 3 Formulations (F3, F5, F9) were selected for Tablet preparation and evaluation. Tablets were prepared with all the three best outcome results of *in-vitro* dissolution of solid dispersions for precise comparison of formulations and coded as Batch A (F3), Batch B (F5), Batch C (F9).

Tablets of Batch A, Batch B, Batch C were prepared using lactose, sodium starch glycolate, microcrystalline cellulose and magnesium stearate and talc. Tablets were evaluated for Hardness, Friability, Weight variation, Content uniformity, Disintegration, *In-vitro* dissolution. The Thickness was found in the range of 2.12 ± 0.36 to 2.40 ± 0.20 mm. The measured Hardness of the tablets of each batch of all formulations was found in the range of 5.2 ± 0.52 to 6.2 ± 0.78 Kg/cm^2. The value of Friability test ranges from 0.37 ± 0.12% to 0.52 ± 0.08%. The Disintegration time was found in the range of 4.46 ± 1.21 to 6.22 ± 1.32 min. The percentage of drug release was found to be 83.53 ± 1.45% to 88.16 ± 1.34%. The *in-vitro* release of Batch C was maximum *i.e.* 88.16 ± 1.34%.

From the above study, Batch C was found to be the Best formulation *i.e.* Optimized formulation. The Optimized Formulation is compared with Marketed Formulation. Stability studies clearly specified that the formulation (Batch C) is highly stable with a shelf life of 916 days. The solid dispersion was stable under accelerated storage conditions.

CONCLUSION: Depending on the experimental data it was concluded that the type of carrier and drug-carrier ratio were the critical factors for the development of solid dispersions. Therefore it was concluded that solid dispersion of Candesartan cilexetil using hydrophilic polymers such as Poloxamer 407, would improve the dissolution rate and solubility of the drug and thereby enhancing its systemic bioavailability.

ACKNOWLEDGEMENT: The authors are grateful to Chairman/Management of PDM Group of Institutions; College of Pharmacy for providing and support for carrying out the research work.

CONFLICT OF INTEREST: There is no conflict of interest / competing interest. This work is original and nothing has been plagiarised to the best of my knowledge.

FINANCIAL ASSISSTANCE: None

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How to cite this article:
Verma P, Singh B and Chaudhary H: Solid dispersion of oral candesartan cilexetil tablets for hypertension: Development and characterisation. Int J Pharm Sci Res 2017; 8(11): 4795-02.doi: 10.13040/IJPSR.0975-8232.8(11).4795-02.