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ISSN: 0975-7538
Research Article

Formulation of liquisolid tablets of candesartan cilexetil

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ABSTRACT

The main objective of present investigation was to enhance the dissolution rate of water insoluble drug Candesartan cilexetil by using liquisolid technique. Liquisolid tablets were prepared using a mathematical model to calculate the required quantities of carrier and coating materials to produce acceptably flowable and compressible admixture. Propylene glycol, PEG 400, Cremophor EL, Capryol 90 and Tween 80 were used as non-volatile liquid vehicles. Avicel PH 102, Aerosil 200 and sodium starch glycolate were employed as carrier, coating material and disintegrant respectively. Drug concentration of 20% w/w (1:4 ratio of drug and liquid vehicle) and 40% w/w (1:2 ratio of drug and liquid vehicle) and R-values (carrier to coating materials ratio) of 10, 20 and 30 were used to formulate the tablets. The formulated liquisolid tablets were evaluated for various parameters including dissolution studies. It was found that the liquisolid tablets formulated with Cremophor EL at drug concentration of 20 % w/w showed higher dissolution profile when compared with other liquisolid formulations, pure drug and directly compressed tablets. The stability studies showed that the dissolution profiles of liquisolid tablets were not affected by ageing significantly. Infrared spectroscopic (IR) and Differential Scanning Calorimetric studies confirmed no interaction exists between drug and excipients. Powder X- ray diffraction studies (PXRD) suggested loss of drug crystallinity upon liquisolid formulation which was further confirmed by scanning electron microscopy (SEM).

Keywords: Candesartan cilexetil; liquisolid tablets; solubility; dissolution rate

INTRODUCTION

Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. The poor solubility of drug substances in the water (Class II and Class IV) and their low dissolution rate in gastrointestinal tract often leads to insufficient bioavailability. The dissolution rate is often the rate-determining step in the absorption site.

Various techniques have been employed to formulate oral drug delivery system that would enhance the dissolution rate and in turn, the absorption efficiency of water insoluble drug such as micronization, lyophilization, co-grinding, formulation of inclusion complexes, prodrug approach, co-solvency, co-crystallisation, solid dispersions, nanonization, inclusion of the drug solution or liquid drug into soft gelatin capsules and liquisolid technology. Among various techniques to overcome the solubility problem, several researchers reported that the formulation of liquisolid tablets was one of the most promising techniques for improving drug dissolution (Vijaykumar Nagabandi, 2011).

Candesartan is a selective AT1 subtype angiotensin II receptor antagonist. Candesartan, ARB, is used alone or with other antihypertensive agents to treat hypertension. It is insoluble in water.

With the liquisolid technology, a liquid may be transformed into a free flowing, dry looking and readily compressible by simple physical blending with the carrier and coating material. Liquisolid tablets of poorly soluble drugs containing a drug solution or drug suspension in a solubilising vehicle show enhanced drug release due to an increased surface area of drug available for release, an increased aqueous solubility of the drug, and an improved wettability of the drug particles. Accordingly, this improved drug release may result in a higher drug absorption in the GIT and thus, an improved oral bioavailability.

MATERIALS AND METHODS

Candesartan cilexetil (Micro Labs Pvt Ltd, Hosur, TN, India); Avicel PH 102, Aerosil 200 and sodium starch glycolate (Kausik Pvt Limited, Chennai, TN, India); Capryol 90 (Gattefosse Pvt Ltd, Mumbai, India) and Cremophor EL (BASF Chemical Company, India) were received as gift samples. Propylene glycol, PEG 400 (CDH Pvt Ltd., New Delhi) Tween 80 (Himedia Laboratories Pvt Ltd., Mumbai), Methanol (Astron Chemicals, Ahmedabad) were purchased from locally. All other chemicals used were of analytical grade.

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Received on: 23-03-2013
Revised on: 22-04-2013
Accepted on: 26-04-2013

Table 1: Φ-value for carrier material and coating material*

Non-Volatile liquid Vehicles	Φ-value for carrier material (Avicel PH102)	Φ-value for coating material (Aerosil 200)
Propylene glycol	0.16	3.31
Polyethylene glycol400	0.005	3.26
Tween 80	0.003	3.95
Cremophor EL	0.18	0.80
Capryol 90	0.16	0.40

*(Amal A.E, 2012 and Vekariya Dhavalkumar, 2012)

Table 2: Composition of candesartan cilexetil liquisolid tablet

Formulation Code with Drug:liquid Vehicle ratio	C_d (%w/w)	R	Liquid vehicle (mg)	Q (mg)	Q (mg)	L_f	Disintegrant (5%) (mg)	Lubricant (0.75%) (mg)	Total Weight (mg)
F1 (1:4)	20%	10	32	81.46	8.14	0.491	6.48	1.02	137.11
F2 (1:4)	20%	20	32	123.07	6.15	0.325	8.46	1.33	179.01
F3 (1:4)	20%	30	32	148.14	4.9	0.270	9.65	1.52	204.21
F4 (1:2)	33.3%	10	16	48.87	4.8	0.491	3.88	0.61	82.16
F5 (1:2)	33.3%	20	16	73.84	3.6	0.325	5.07	0.79	107.30
F6 (1:2)	33.3%	30	16	88.88	2.9	0.270	5.78	0.91	122.47
F7 (1:4)	20%	10	32	100.5	10.8	0.398	7.55	1.18	159.73
F8 (1:4)	20%	20	32	200.0	10	0.200	12.5	1.96	264.21
F9 (1:4)	20%	30	32	300.75	9.38	0.133	17.50	2.75	370.38
F10 (1:2)	33.3%	10	16	60.30	6.48	0.398	4.76	0.75	95.84
F11 (1:2)	33.3%	20	16	120.0	6	0.200	7.5	1.18	158.68
F12 (1:2)	33.3%	30	16	180.45	5.63	0.133	11.30	1.78	239.16
F13 (1:4)	20%	10	32	120.84	12.08	0.331	8.64	1.36	182.92
F14 (1:4)	20%	20	32	238.09	11.90	0.168	14.49	2.28	306.66
F15 (1:4)	20%	30	32	353.98	11.79	0.113	20.28	3.19	429.24
F16 (1:2)	33.3%	10	16	72.50	7.25	0.331	5.18	0.81	109.74
F17 (1:2)	33.3%	20	16	142.85	7.14	0.168	8.69	1.36	183.94
F18 (1:2)	33.3%	30	16	212.38	7.07	0.113	12.17	1.91	257.53

Active ingredient 8 mg in all formulation; Non-volatile liquid vehicle in F1-F6 PG, F7-F12 Tween80, F13-F18 PEG400

Solubility studies

The solubility of Candesartan cilexetil was carried out in Propylene glycol (PG), Polyethylene glycol 400 (PEG 400), Tween 80, Cremophor EL (Polyoxyl 35 castor oil), Capryol 90 (Propylene glycol monocaprylate) and in distilled water. Saturated solutions in respective solvents were prepared by adding an excess amount of drug and rotated for 48 hours at 25°C using a mechanical shaker. The filtered supernatants were further diluted with distilled water (10µg/ml) and analyzed with a UV/visible spectrophotometer (shimadzu UV-1700 pharma spec, Japan) at 257nm. The solubility of Candesartan Cilexetil in the respective liquid vehicle was calculated using calibration curve. Each experiment was carried out in triplicate (Nokhodchi A, 2005)

Infrared (IR) spectroscopic studies

Infrared Spectrum of Candesartan cilexetil, excipients, non-volatile liquid vehicles, physical mixtures and liquisolid formulation were recorded by KBr disc method using infrared Spectrophotometer (FT-IR 8400s Shimadzu, Japan). Spectra were analyzed for drug-polymer interaction. (Yadav A.V, 2010).

Differential Scanning Colorimetric studies

Thermogram of Candesartan cilexetil, excipients, physical mixture and liquisolid formulation were recorded by using Differential Scanning Colorimeter. The equipment was calibrated using indium and zinc. Samples were heated at 10°C per min in aluminium pans under nitrogen atmosphere. The cell and sample were then heated to 250°C while monitoring heat flow (Vijaykumar Nagabandi, 2011).

Procedure for preparation of liquisolid tablets

Candesartan Cilexetil liquisolid formulations (F1 to F30) were prepared using Propylene glycol, PEG 400, Tween 80, Capryol 90 and Cremophor EL, as liquid vehicles with two different drug concentrations, 20%w/w and 33.3%w/w. The composition of all the formulations was given in Table.2 (A & B). Drug was dispersed in the liquid vehicle with continuous mixing using magnetic

Table 3: Composition of candesartan cilexetil liquisolid tablet

Formulation Code with Drug:liquid Vehicle ratio	C_d (%w/w)	R	Liquid vehicle (mg)	Q (mg)	Q (mg)	L_f	Disintegrant (5%) (mg)	Lubricant (0.75%) (mg)	Total Weight (mg)
F19 (1:4)	20%	10	32	200	20	0.200	13	2.04	275.04
F20 (1:4)	20%	20	32	222.2	11.11	0.180	13.6	2.15	289.99
F21 (1:4)	20%	30	32	231.2	7.70	0.173	13.9	2.19	294.99
F22 (1:2)	33.3%	10	16	120	12	0.200	7.8	1.14	164.94
F23 (1:2)	33.3%	20	16	133.3	6.6	0.180	8.1	1.29	173.38
F24 (1:2)	33.3%	30	16	138.7	4.62	0.173	8.36	1.31	176.35
F25 (1:4)	20%	10	32	153.8	15.38	0.26	10.45	1.64	221.24
F26 (1:4)	20%	20	32	181.8	9.09	0.22	11.54	1.81	244.24
F27 (1:4)	20%	30	32	200	6.66	0.20	12.33	1.94	260.93
F28 (1:2)	33.3%	10	16	92.30	9.23	0.26	6.27	0.98	132.7
F29 (1:2)	33.3%	20	16	109.09	5.45	0.22	6.92	1.09	146.55
F30 (1:2)	33.3%	30	16	120	4.0	0.20	7.4	1.16	156.56
DCT	-	30	-	200	6.66	-	10.73	1.690	227.08

Active ingredient 8 mg in all formulation; Non-volatile liquid vehicle in F19-F24 Capryol 90, F25-F30 Crem EL

R = Carrier and coating material ratio, Q = W/L_f (Q= Carrier material and W=Total weight of drug and liquid vehicle), q=Q/R (q = Coating material), L_f =Liquid load factor, Crem El = Cremophor EL, C_d = Drug concentration in liquid medication (% w/w). [C_d = wt. of drug / wt. of drug +wt.ofliquid x 100], DCT= Directly compressed tablets

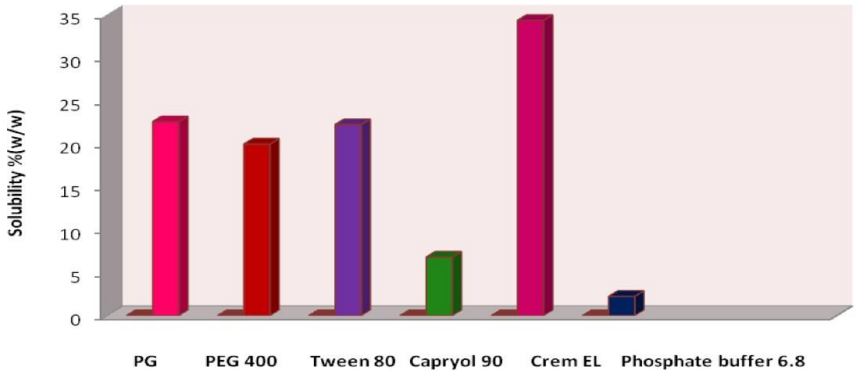

Figure 1: Solubility of Candesartan cilexetil in various non volatile liquid vehicles

stirrer to produce the liquid medication. All liquid formulations contained Avicel PH102 (microcrystalline cellulose) as the carrier powder and Aerosil 200 (Silica) as the coating material at a fixed powder ratio (R) of 30:1, 20:1 and 10:1. The appropriate amounts of the carrier and coating materials used in the liquisolid formulation were derived from their Φ-value (flowable liquid-retention potential value) and liquid load factors (L_f). L_f can be calculated by substituting the flowable liquid-retention potential of the carrier (Φ_{CA}-value) and flowable liquid-retention potential of the coating material (Φ_{CO}-value) into Eq (1). Flowable liquid retention potential of the excipients was reported in the Table 1. By knowing liquid load factors (Lf) and amount of liquid medication (W), appropriate amounts of carrier material (Q) and coating material (q) can be calculated using Equations. (2) and (3)

$$Lf = \Phi_{CA} + \Phi_{CO} \times 1/R \quad (1)$$

$$Lf = W/Q \quad (2)$$

$$R = Q/q \quad (3)$$

The appropriate amount of Avicel PH102 was mixed with the drug-vehicle suspension. Aerosil 200 was then added to convert the wet mixture into dry powder under continuous mixing in the mortar and pestle. Finally, a 5%w/w of sodium starch glycolate as a disintegrant and 0.75% w/w of magnesium stearate as a lubricant were added into the mixture and mixed for 10 min. The final mixture was compacted on a 10mm flat-faced punch and die set using a single punch tableting machine each batch consisted of 60 tablets. (Amal A.E, 2009 and Lakshmi P.K, 2011).

Preparation of directly compressed tablets

A conventional formulation of Candesartan cilexetil (DCT) were also prepared by using drug, Avicel PH 102, Aerosil 200, sodium starch glycolate and magnesium stearate, (without addition of any non-volatile liquid vehicles). The composition of the formulation was given in Table**.** 2B. All the ingredients were mixed in the mortar for 10 min and final mixture was directly com-

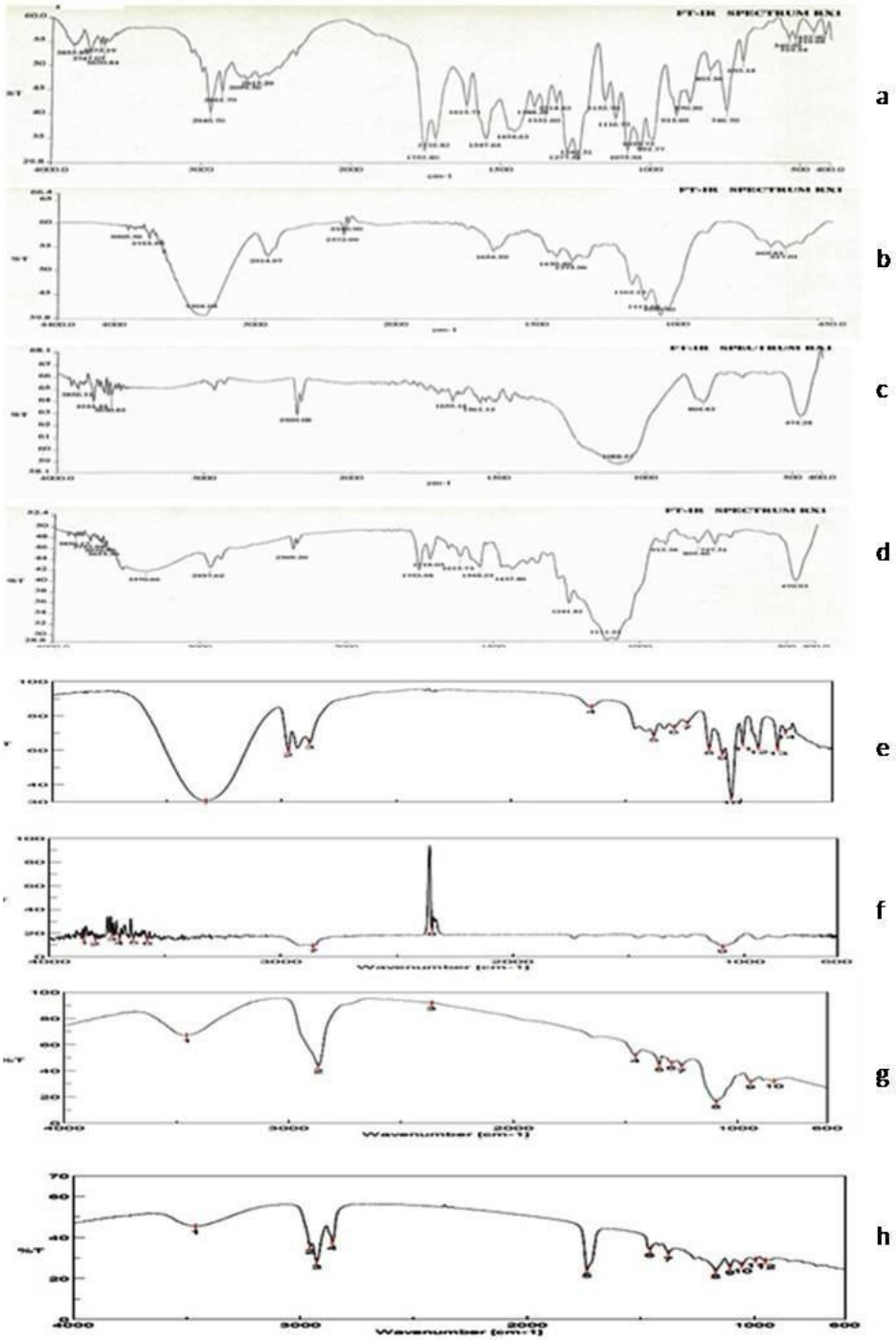

Figure 2: FT-IR Spectrum of (a) Candesartan cilexetil (b) Microcrystalline cellulose (MCC) (c) Aerosil 200 (d) Pure drug + MCC + Aerosil 200 (e) Propylene glycol (f) Tween 80 (g) Polyethylene glycol 400 (h) Capryol 90

pressed using a single punch tabletting machine. (Aparna.C, 2011).

Flow properties for liquisolid powder

Flow properties of the powder were determined by angle of repose, bulk density, tapped density, carr's index and hausner's ratio.

Evaluation of liquisolid tablets

The prepared liquisolid tablets were evaluated for content uniformity, thickness, hardness, weight variation, friability, disintegration time and in vitro release studies. All tests were carried out according to the IP specifications. All the studies were done in triplicate.

***In vitro* release studies**

In vitro release studies was performed by using USP type II Paddle dissolution apparatus in 900 ml of phosphate buffer pH 6.8 maintained at 37° C ± 1° C and 50 rpm. Samples (5 ml) were withdrawn at regular intervals of 10 minutes for 1hr and the same volume of fresh dissolution medium was replaced after every withdrawal. The withdrawn samples were analyzed by UV- visible spectrophotometer at 257nm. (Yadav A.V, 2010).

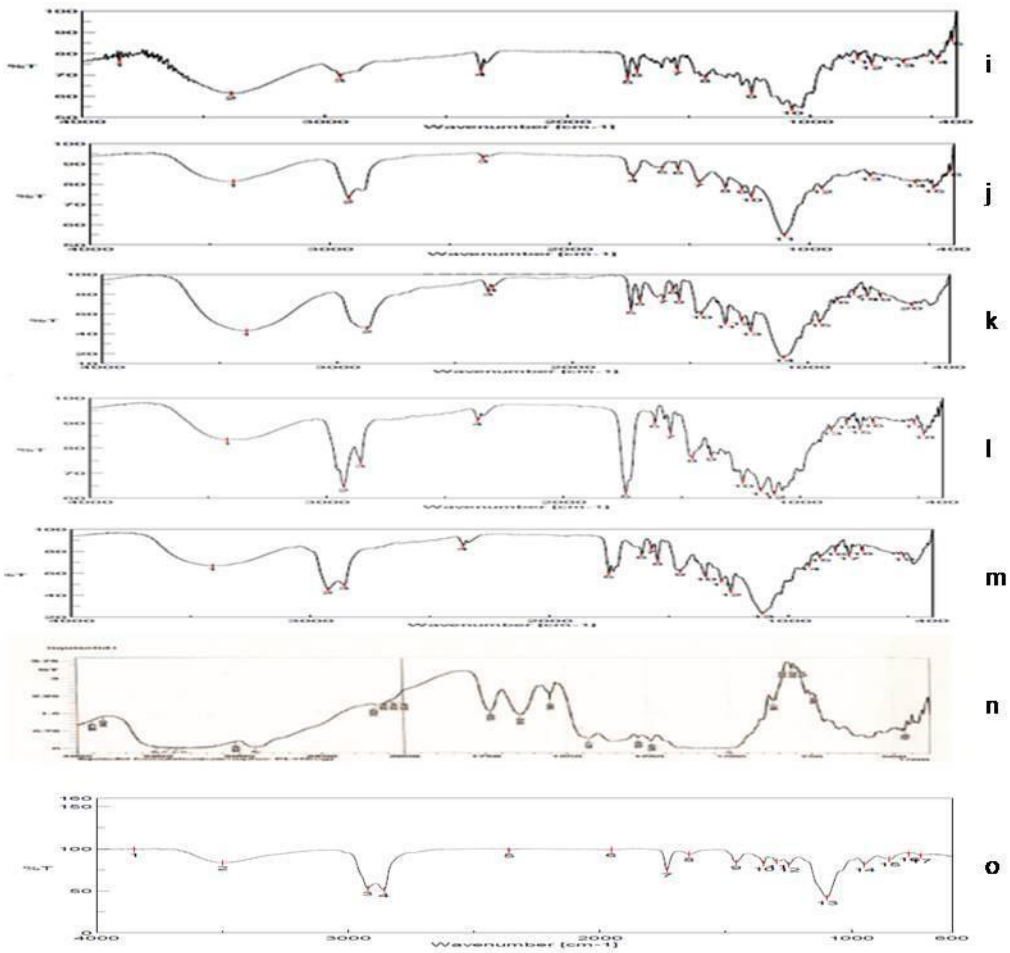

Figure 3: FT-IR Spectrum of (i) Drug+Propylene glycol+ aerosil 200 + MCC (j) Drug+Tween 80+ aerosil 200 + MCC (k) Drug+Polyethylene glycol 400+ aerosil 200 + MCC (l) Drug+capryol 90 + aerosil 200 + MCC (m)Drug+Cremophor EL+ aerosil 200 + MCC (n) Liquisolid formulation (o) Cremophor EL

Assessment and comparison of drug dissolution rates

The dissolution rate of Candesartan cilexetil is the amount of drug (in µg) dissolved per minute by each tablet formulation during first 10 min is calculated by the following equation (Shashidher Burra, 2011).

$$D_R \frac{(M \times D)}{1000}$$

Where,

M = Total amount of pure drug in each tablet (in µg)

D = Percentage of drug dissolved in the first 10 minutes

Powder X-ray diffraction studies

Powder X-ray diffraction pattern of Candesartan cilexetil, excipients, physical mixture and liquisolid formulation were studied using X-ray diffractometer (XRD-462, Digaku, Japan) with CuKα radiation. Voltage and current were set 40 kV and 30 mA respectively. All pattern scanned over range 5-70^o 2θ angle with a scan speed of 10^o/min. (Vijaykumar Nagabandi, 2011)

Scanning electron microscopy (SEM)

SEM was used to assess the morphological characteristics of liquisolid tablets. The samples were fixed on aluminium stubs with double-sided tape, gold coated sputter examined in the microscope using an accelerating voltage of 15 KV, at a working distance of 8 mm and magnification of X10000 (Fahmy R.H, 2008).

Stability studies

The best formulation of three batches was stored at 40° C ± 2°C and RH 75%± 5% for three months. The in vitro release studies, drug content, physical appearance, hardness and thickness of stored formulations were compared with those of freshly prepared tablets. (Prasanth Sai R.V, 2011 and Nokhodchi A, 2007).

RESULTS AND DISCUSSION

Solubility studies

The solubility of drug in various non-volatile liquid vehicles such as Propylene glycol, PEG 400, Tween 80, Cremophor EL, Capryol 90 and in Phosphate buffer 6.8 was 22.2±0.36%, 19.94±0.59%, 22.54±0.52%, 34.32±0.42%, 6.80±0.16% and 2.2±0.28% w/w respectively were shown in Figure.1. From the results, it was observed that the solubility of drug in Cremophor EL was higher when compared with other liquid vehicles which may be due to the highest hydrophilicity and polarity (Amal Ali Elkordy, 2012).

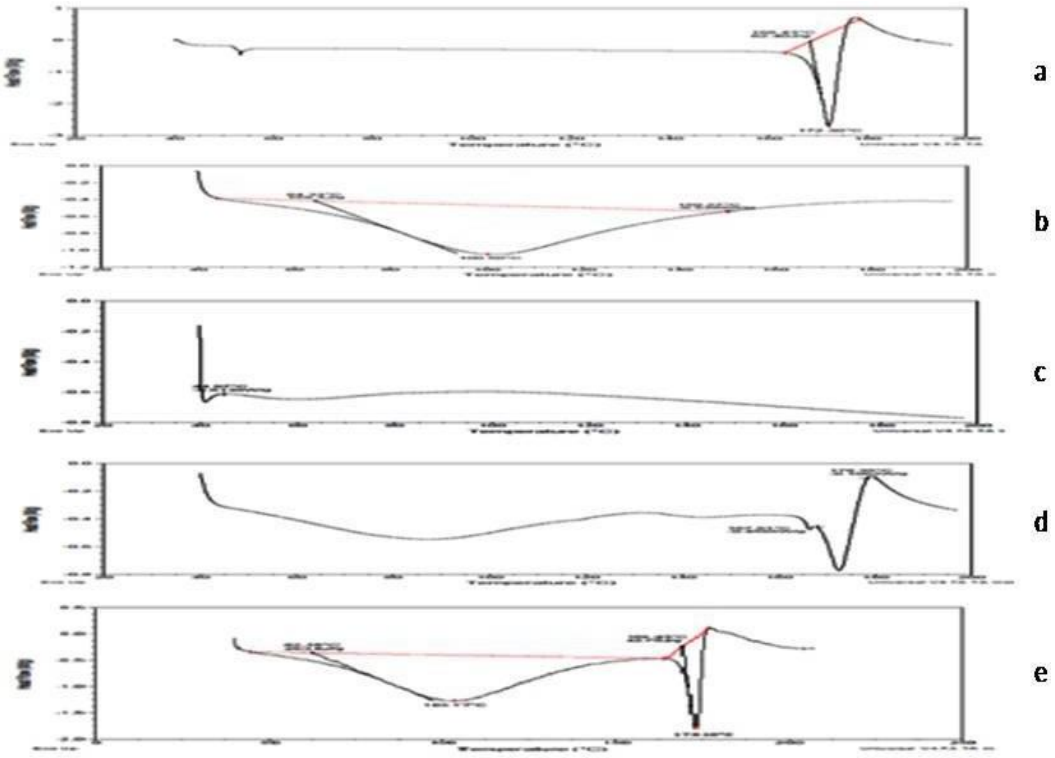

Figure 4: DSC thermogrm of (a) Candesartan cilexetil (b) Microcrystalline cellulose (c) Aerosil 200 (d) Physical mixture (e)Liquisolid formulation

Infrared Spectrum of Candesartan cilexetil, excipients, non-volatile liquid vehicles, physical mixtures and liquisolid formulation were shown in Figure.2. Infrared spectrum of pure drug showed the characteristic peaks at 2940.70 cm^{-1}, 1752.80 cm^{-1}, 1716.32 cm^{-1}, 1547.64 cm^{-1}, 870.20 cm^{-1}. Further in the physical mixtures and liquisolid formulation, all the above characteristics peaks of the drug appeared in the spectrum, which indicated that there was no interaction between the drug and polymers in the physical mixtures and formulation.

Differential Scanning Colorimetric studies

Thermogram of Candesartan cilexetil showed a sharp endothermic peak at 172.30˚C corresponding to its melting temperature. Such sharp endothermic peak signifies that Candesartan cilexetil used was in pure crystalline state. Microcrystalline cellulose showed sharp endothermic peak at 100.50°C. The thermal behavior of aerosil 200 did not show any sharp endothermic peak and hence, the aerosil 200 was in an almost amorphous state. The sharp endothermic peak of pure drug was not observed in physical mixture and liquisolid formulation, which indicates that the Candesartan cilexetil was molecularly dispersed and in an amorphous form. (Sanjeev Gubbi, 2009).The thermogram of pure drug, excipients, physical mixture and liquisolid formulation were shown in Figure.3

Precompression studies for liquisolid powder

Flow properties such as angle of repose, bulk density, tapped density, Carr's index and hausner's ratio were represented in the Table 3. The angle of repose of all the prepared formulations was in the ranges from 17.09° to 28.32°, which indicates the good flow properties of liquisolid powder. The Carr's index of all the formulations was found to be in range of 14.78 % to 25.06%. It was less than 25%, which indicating a good flow. Hausner's ratio of all the formulations up to 1.25 was considered acceptable as a flow property.

Evaluation of liquisolid tablets

The liquisolid formulations and directly compressed tablets were subjected to various evaluation tests such as thickness, hardness, drug content, uniformity of weight, friability and disintegration time were represented in the Table.4. The hardness of all the formulations was found to be in the range of 3 to 4.5 Kg/cm^2, which indicates that all the tablet formulations had good mechanical strength. The drug content was found to be in the range of 98.03% to 99.82%, which indicates all the formulations were within the acceptable limits as per IP (Limits: Content uniformity not less than 85% and not more than 115 %). In a weight variation test, the average percentage deviation of all the tablet formulation was found to be within the IP limit and hence passed the uniformity of weight. The percentage friability of all the tablet formulations was found to be in the range of 0.20 to 0.87 %, it was less than 1%. The results indicated that all the tablet formulation had a good mechanical resistance of tablets. Disintegration time of all the prepared tablet formulations was found to be 3 min 49 sec to 12 min 26 sec. It

Table 4: Precompressional evaluation of powder blend

Formulation code	Angle of repose θ ±SD	Bulk density (gm/ml) ± SD	True density (gm/ml) ± SD	Carr's index (%) ± SD	Hausner's ratio ± SD	Drug content ± SD (%)
F1	18.18±0.434	0.476±0.004	0.616±0.0047	22.69±0.78	1.20±0.016	95.41±0.75
F2	25.59±0.704	0.543±0.0047	0.716±0.014	24.49±0.79	1.12±0.014	96.12±0.28
F3	18.91±0.372	0.466±0.0047	0.603±0.0047	22.63±0.708	1.18±0.009	96.47±0.76
F4	24.54±0.452	0.506±0.0023	0.683±0.0047	24.87±0.60	1.14±0.012	98.46±0.334
F5	20.96±.0.97	0.523±0.0047	0.696±0.29	25.85±0.621	1.22±0.0012	96.03±0.16
F6	26.17±0.960	0.490±.0.00	0.606±0.0047	20.1±0.60	1.14±0.0009	99.05±0.164
F7	25.61±0.32	0.496±0.004	0.683±0.056	26.06±0.94	1.21±0.0009	97.99±0.16
F8	22.80±0.40	0.340±0.00	0.450±0.00	24.4±0.00	1.22±0.00	97.76±0.32
F9	25.71±0.38	0.448±0.002	0.584±0.005	23.22±0.30	1.19±0.0047	98.47±0.16
F10	23.86±0.21	0.468±0.003	0.593±0.004	21.4±0.07	1.07±.0009	98.59±0.4
F11	26.18±.030	0.506±0.30	0.635±0.01	20.24±0.34	1.22±0.02	99.17±0.32
F12	24.5±0.99	0.534±0.01	0.677±0.01	21.06±0.05	1.06±0.002	99.40±0.32
F13	23.99±0.4	0.387±0.0004	0.498±.0004	22±0.00	1.18±0.002	99.05±0.16
F14	25.78±0.9	0.493±0.009	0.638±0.009	22.7±0.004	1.09±0.41	98.47±0.15
F15	18.23±0.45	0.530±0.003	0.622±0.003	14.78±0.60	1.17±0.008	99.79±0.49
F16	19.74±0.67	0.426±0.003	0.540±0.003	21.07±0.39	1.24±0.009	99.17±0.16
F17	18.51±0.9	0.434±0.003	0.539±0.004	19.57±0.35	1.23±0.009	99.19±0.4
F18	17.09±0.92	0.522±0.002	0.656±0.004	20.42±0.38	1.25±0.004	99.17±0.16
F19	25.38±0.62	0.396±0.001	0.497±0.004	20.97±0.04	1.24±0.009	99.4±0.16
F20	25.40±0.37	0.333±0.001	0.416±0.001	19.6±0.43	1.24±.043	99.76±0.16
F21	25.71±0.38	0.446±0.002	0.572±0.0023	22±0.64	1.23±0.01	99.7±0.18
F22	24.67±0.38	0.417±0.002	0.524±0.006	20.46±0.62	1.21±0.05	99.52±0.16
F23	28.23±0.6	0.326±0.0016	0.418±0.003	22±0.03	1.20±0004	98.82±0.32
F24	28.03±0.3	0.332±0.0047	0.420±0.004	20.85±0.64	1.25±0.021	98.23±0.18
F25	23.21±0.4	0.270±0.002	0.343±0.002	21.43±.0081	1.21±0.004	99.17±0.16
F26	22.86±0.18	0.333±0.0018	0.418±0.0058	20.24±0.45	1.24±0.009	98.47±0.169
F27	23.87±0.14	0.301±0.0012	0.375±0.0016	19.64±0.066	1.24±0.018	99.82±0.16
F28	24.87±0.12	0.424±0.0023	0.539±0.0037	21.3±0.11	1.25±0.004	98.70±0.16
F29	23.55±0.19	0.307±0.0024	0.399±0.0029	22.76±0.40	1.20±0.0004	97.8±0.285
F30	28.22±0.69	0.324±0.009	0.413±.0020	21.44±0.20	1.25±0.004	97.7±0.16
Directly compressed tablets	20.48±0.36	0.523±0.0023	0.656±0.0032	20.22±0.12	1.253±0.0023	96.4±0.234

n=3*

was lesser than 15 min, which indicates all the formulations were within the acceptable limits as per IP.

***In vitro* release studies**

The in vitro release studies showed that the release profiles of different formulations varied according to the vehicle type, drug concentration in the liquid medication (ratio of drug and liquid vehicle) and ratio of microcrystalline cellulose & aerosil 200 (R-value). The results of *in vitro* release studies from liquisolid formulations were shown in Figure: 4 (a to j).

Formulations were prepared with Propylene glycol (F1-F6), Tween80 (F7-F12), Polyethylene glycol 400 (F17-F18), Capryol 90 (F19-F24), Cremophor EL (F25-F30) showed the cumulative percentage drug release of 82.43% to 90.68%; 85.95% to 91.25%; 73.4% to 83.31%; 64.91% to 74.4%; 92.18% to 99.5% respectively at the end of 1 hour.

The relatively poorer *in vitro* release profile of formulations were prepared with Propylene glycol (F1-F6), Tween 80 (F7-F12), Polyethylene glycol 400 (F13-F18) and Capryol 90 (F19- F24) may be due to the lower solubility of drug in these liquid vehicles as compared to those in Cremophor EL (F25-F30). Formulations F25, F26 and F27 were prepared with 1: 4 ratio of drug and Cremophor EL (it contains more amount of liquid vehicle) and 10:1, 20:1, 30:1 ratio of MCC & aerosil 200 showed the cumulative percentage drug release of 95.12%, 96.8% and 99.5% respectively at the end of 1 hour. Formulations F28, F29 and F30 were prepared with 1: 2 ratio of drug and Cremophor EL (it contains less amount of liquid vehicle) and 10:1, 20:1, 30:1 ratio of MCC & aerosil 200 showed the cumulative percentage drug release of 92.02%, 92.18% and 93.23% respectively at the end of 1 hour.

Table 5: Post compressional evaluation of liquisolid tablets

Formulation code	Hardness (kg/cm²)	Thickness (mm)	Weight variation (mg)	Friability (%)	Disintegration Time	Drug content ± SD (%)
F1	3	2.3	120.9 - 141.46	0.853	7 min 90 sec	98.70±0.16
F2	3	2.5	161.69 - 188.53	0.843	7 min 11 sec	98.94±0.28
F3	4.5	3.1	188.17 - 216.9	0.69	8 min 19 sec	99.29±0.285
F4	3	2.5	73.95 - 90.47	0.773	5 min 41 sec	99.06±0.164
F5	3	2.5	92 - 113.4	0.80	6 min 93 sec	98.70±0.164
F6	3	2.5	106.57 - 131.05	0.383	7 min 35 sec	98.58±0.289
F7	3	3	156.14 - 183.56	0.279	8 min 90 sec	99.17±0.436
F8	4	4.3	241.36 – 281.48	0.309	8 min 86 sec	99.52±.164
F9	3	3.4	331.52 – 366.54	0.206	9 min 69 sec	98.82±0.32
F10	3	2	89.16 – 109.52	0.610	5 min 10 sec	98.35±0.169
F11	3	2.5	145.89 – 169.69	0.480	7 min 14 sec	98.47±0.169
F12	3	3.2	193.7 – 225.2	0.281	7 min 94 sec	98.35±0.169
F13	3	3	165.85 – 193.27	0.790	7 min 87 sec	98.35±0.334
F14	4.5	3.2	290.22 – 320.88	0.320	12 min 26 sec	99.52±0.164
F15	4.5	4.5	326.6 – 429.52	0.230	8 min 11 sec	99.40±0.164
F16	3	2.5	97.09 – 119.03	0.870	3 min 49 sec	98.70±0.164
F17	3	3	168.3 – 195.88	0.600	4 min 67 sec	99.52±0.164
F18	4	4	237.59 – 276.21	0.440	5 min 13 sec	99.05±0.329
F19	3.5	4	252.63 – 293.8	0.420	6 min 23 sec	98.47±0.169
F20	3.5	4.2	266.73 – 310.09	0.430	6 min 91 sec	99.52±0.334
F21	4	4.5	271.25 – 315.49	0.370	7 min 13 sec	99.40±0.164
F22	3	2.6	151.05 – 175.79	0.490	5 min 93 sec	98.82±0.239
F23	3	2.4	160.21 – 186.21	0.51	5 min 95 sec	98.47±0.169
F24	3	2.5	162.52 – 188 96	0.56	6 min 05 sec	98.11±0.164
F25	3.5	3.3	206.25 – 239.43	0.55	6 min 23 sec	98.47±0.169
F26	4.5	4	225.2 – 261.82	0.49	6 min 55 sec	98.58±0.499
F27	4.5	4	240.53 – 279.65	0.48	7 min 11 sec	99.76±0.169
F28	3	2.5	118.21 – 144.47	0.73	4 min 43 sec	98.47±0.169
F29	3	2.5	130.71 – 159.75	0.69	5 min 03 sec	98.70±0.164
F30	3	2.5	140.4 – 171.41	0.64	5 min 51 sec	98.82±0.164
Directly compressed tablets	5	4	247.35-273.37	0.39	13 min 20 sec	95.3%±0.16

n=3*; General appearance is White colour

The overall results indicated that the prepared liquisolid tablet formulations F27 comprised of cremophor EL, 1:4 ratio of drug & liquid vehicle and 30:1 ratio of MCC & aerosil 200 (high amount of MCC -- act as disintegrant agent, low amount of aerosil 200 -- hydrophobic in nature that would retard drug release) which improved the dissolution behavior of drug. (Amal Ali Elkordy, 2012, Ali Nokhodchi, 2007).

Comparison of dissolution studies of best formulation with pure drug and directly compressed tablet (DCT)

The *in vitro* dissolution studies of formulation (F27)(1:4) containing Cremophor EL showed the drug release of 99.5% in 1 hour when compared to the pure drug (24.2%), and directly compressed tablet (50.4%) were shown in Figure.5

Assessment and comparison of drug dissolution rates

The comparison of dissolution rate for pure drug, directly compressed tablets and liquisolid formulation were shown in Figure.6. The dissolution rate of pure drug, directly compressed tablets and liquisolid formulation were showed 66.56µg/min, 104.32µg/min and 319.04µg/min respectively at the first 10 min. The dissolution rate of liquisolid formulation was increased which may be due to high molecular dispersion states of the drug in the formulation (Nokhodchi A, 2005).

Powder X-ray diffraction studies

The crystalline nature of drug was studied by the characteristic PXRD pattern which showed sharp peaks at 9.84, 17.05 and 23.19 at 2θ. PXRD for pure drug, excipients, physical mixture and liquisolid systems were showed in Figure: 7. Avicel pH 102 has a sharp characteristic peak at 22.78 at 2θ while liquisolid formulation powder and physical mixture obtained only one sharp characteristic peak at 22.30 & 22.60 at 2θ respectively, which is evidence that Avicel pH 102 maintained its crystalline state. Liquisolid PXRD pattern showed absence of these characteristic peaks of drug, which indi-

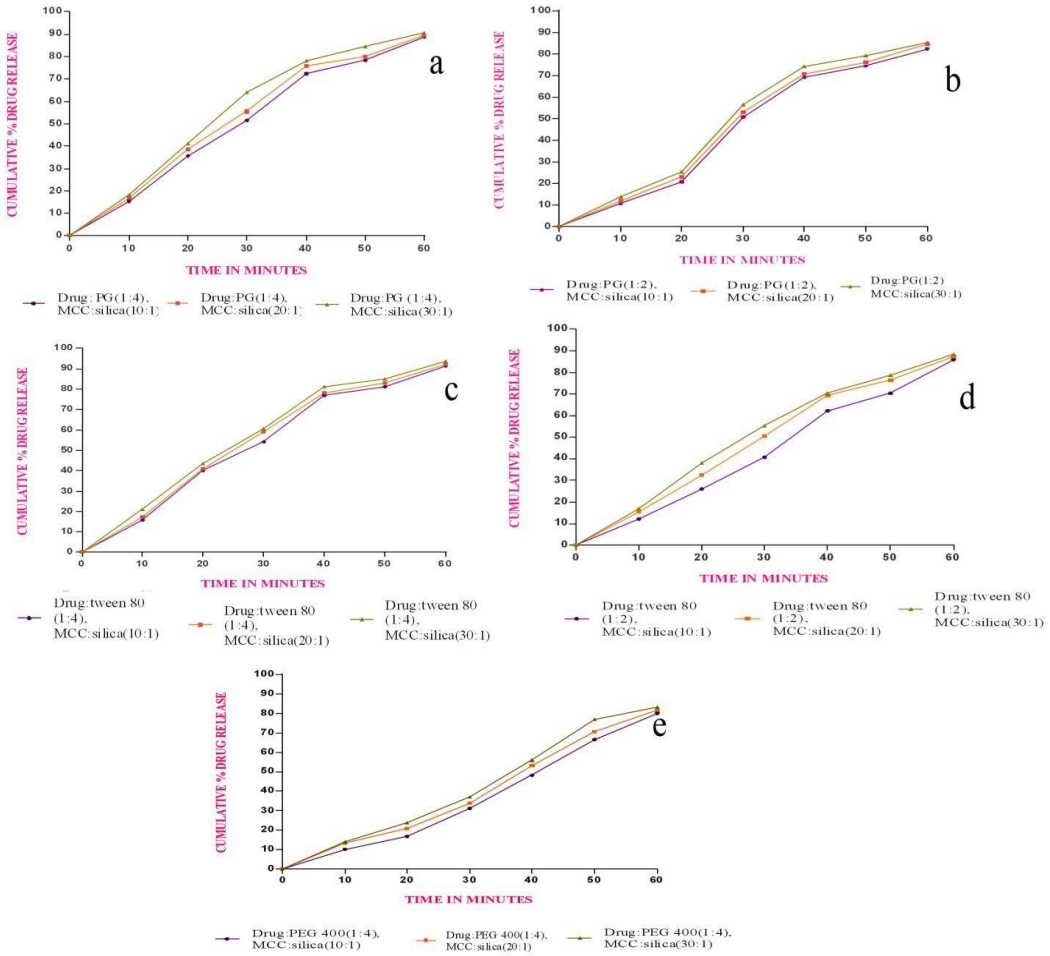

Figure 5: In vitro release of Candesartan Cilexetil liquisolid tablets (a) Drug:PG (1:4), (b) Drug:PG (1:2), (c) Drug:Tween 80 (1:4) (d) Drug:Tween80 (1:2) (e) Drug:PEG400 (1:4)

cated pure drug, was entirely converted into amorphous or solubilized from. The absence of crystalinity in the liquisolid formulation might be due to solubilization of drug in liquid vehicle that is possibly absorbed and adsorbed on the carrier and coating material. The amorphization of pure drug may result in an enhancement of dissolution rate (Sanjeev Ragavendra Gubbi, 2010).

Scanning electron microscopy analysis

The surface morphology of liquisolid tablets was scanned using scanning electron microscopy was shown in Figure.8. The photomicrographs of the liquisolid system signify the complete disappearance of Candesartan cilexetil crystals. It indicates that the drug was completely solubilized in liquisolid system and also indicates that even though the drug is in solid dosage form, it is held within the powder substrate in solution, almost molecularly dispersed state, which contributes to enhanced dissolution rate of drug (Karmarkar A.B, 2009).

Stability studies

The best formulation of three batches was stored at 40° C ± 2°C and RH 75%± 5% for three months. The results showed no significant changes in physical appearance, hardness, thickness, drug content and in vitro dissolution test of aged tablets compared to the fresh liquisolid tablets. This indicates that the liquisolid tablets were stable under these storage conditions. (Table.5A &5B).

CONCLUSION

The liquisolid tablet technique can be effective way for dissolution rate improvement of water insoluble drugs such as Candesartan cilexetil. The liquisolid tablets prepared with Cremophor EL showed higher dissolution rate in comparison with formulations prepared with other liquid vehicles and directly compressed tablets. The results showed that dissolution rate of the drug from liquisolid tablets were affected by ratio of the MCC & aerosil 200 and ratio of drug & liquid vehicles. Enhanced dissolution rate obtained in the present study due to increased wetting and surface area available for dissolution. This novel approach to the formulation may be helpful to improve oral bioavailability.

ACKNOWLEDGEMENT

The authors are thankful to the Microlabs Pvt Limited, Hosur, India for providing gift sample of the Candesartan cilexetil. The authors are very greatful to the Dean,

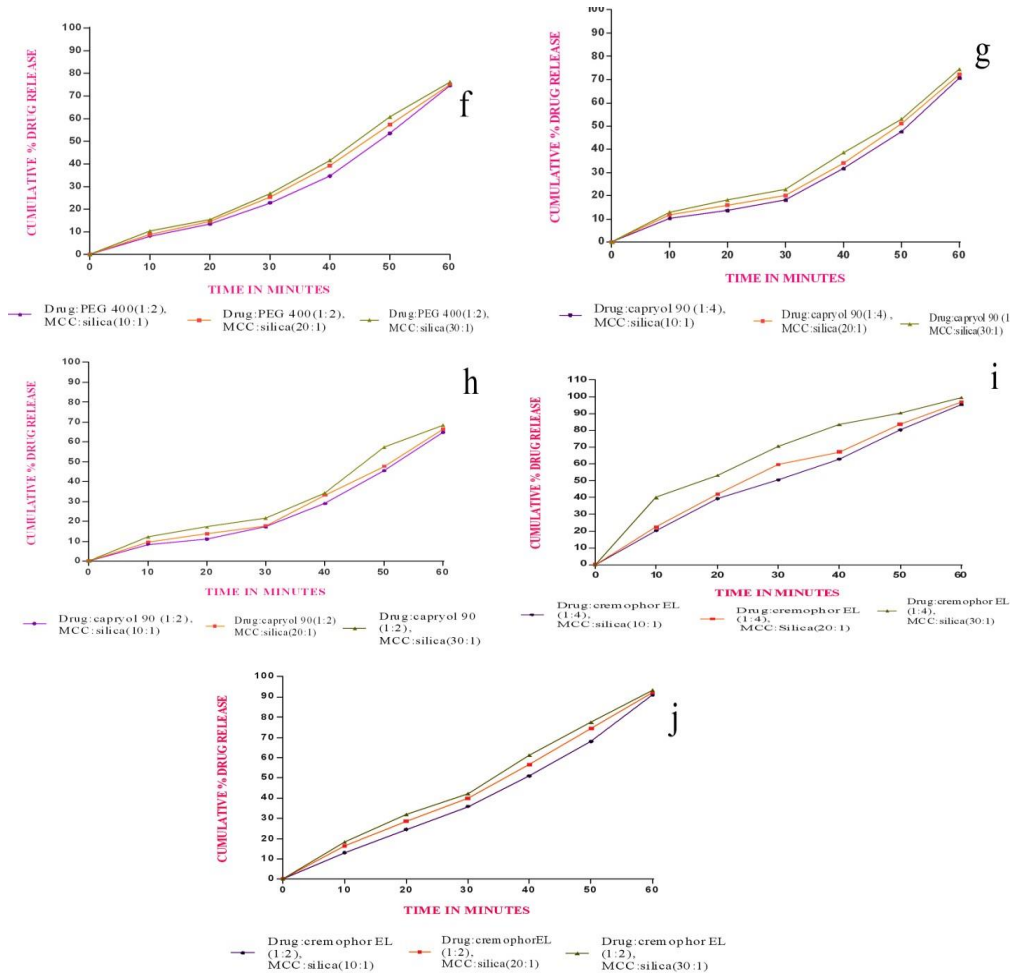

Figure 6: In vitro release of Candesartan Cilexetil liquisolid tablets (f) Drug:PEG400 (1:2) (g) Drug:Capryol 90 (1:4) (h) Drug:Capryol 90 (1:2), (i) Drug:Cremophor EL (1:4) (j) Drug:Cremophor EL (1:2)

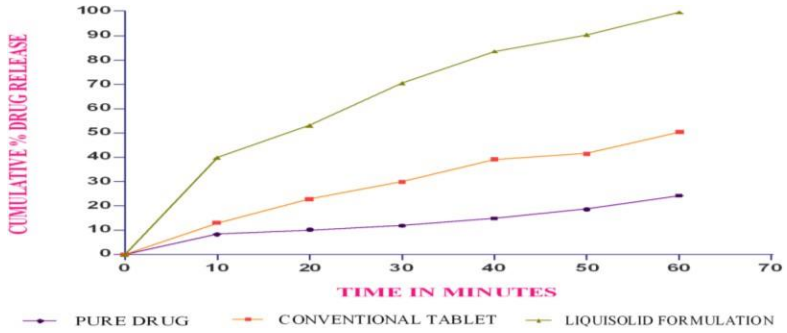

Figure 7: Comparison of in vitro release studies liquisolid formulation with pure drug and DCT

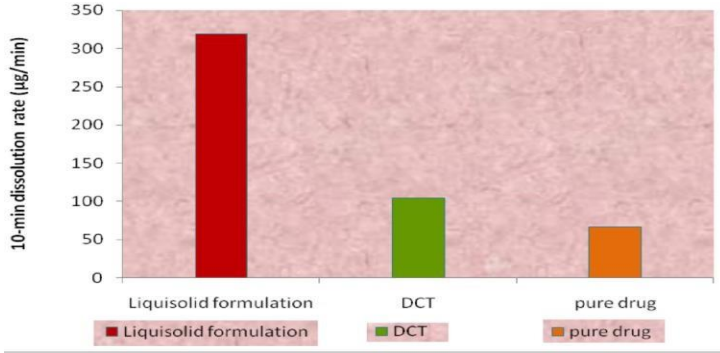

Figure 8: Comparison of the 10-min dissolution rate of pure drug, DCT and liquisolid tablet

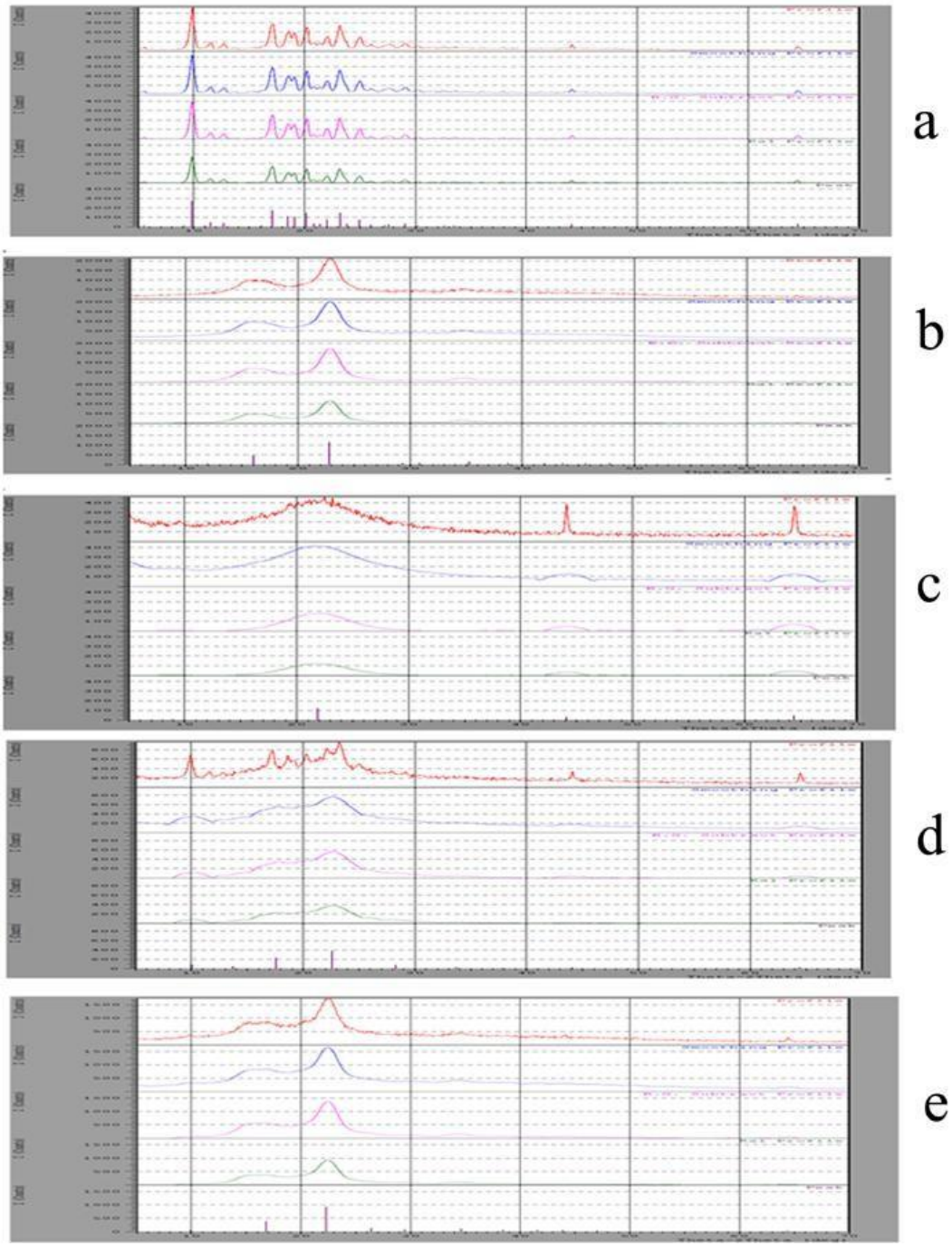

Figure 9: Powder x- ray diffraction studies of (a) Candesartan cilexetil (b)Microcrystalline cellulose (c) Aerosil 200 (d) Physical mixture (e) Liquisolid formulation

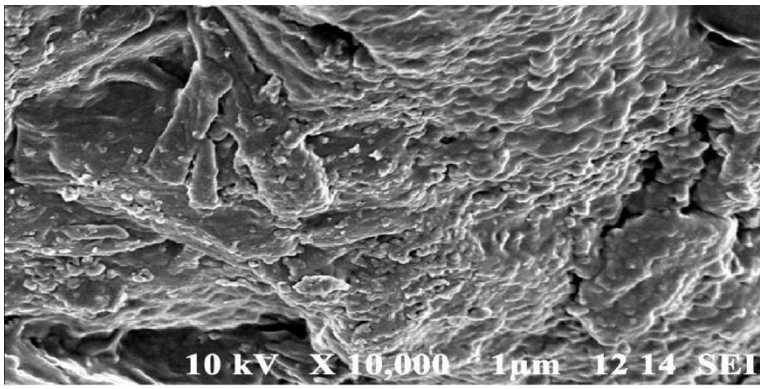

Figure 10: SEM of liquisolid tablet

Table 6: Stability study of best formulation (F27) at 40° C ± 2°C and RH 75%± 5%

Parameters	Interval of testing			
	At 0 Month	At 1month	At 2 Month	At 3 Month
Physical appearance	White colour, biconvex shaped	White colour, bi-convex shaped	White colour, bi-convex shaped	White colour, bi-convex shaped
Hardness(kg/cm^2)	4.5	4.5	4.5	4.5
Thickness (mm)	4	4	4	4
Drug content (%)±SD	99.86±0.169	99.42±0.329	99.14±0.164	99.05±0.254

Table 7: In vitro dissolution profile of best formulation (F27) at 40° C ± 2°C and RH 75%± 5%

Time interval (min)	Cumulative Percentage of drug release ± SD			
	AT 0 month	AT 1 month	AT 2 month	AT 3 month
10	39.88±0.372	39.67±0.362	39.67±0.362	39.18±0.371
20	53.16±0.215	52.62±0.315	52.29±0.372	52.16±0.206
30	70.48±0.372	70.08±0.064	70.11±0.091	69.98±0.275
40	83.42±0.214	83.33±0.311	83.23±0.077	83.11±0.372
50	90.34±0.373	89.97±0.370	89.8±0.468	89.59±0.260
60	99.5±0.217	99.38±0.375	99.18±0.123	99.07±0.209

Principal, Department of Pharmaceutics, College of Pharmacy, Madurai Medical College, Madurai-20, Tamil Nadu, India, for providing facilities and constant encouragement.

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