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FORMULATION AND OPTIMIZATION OF MOUTH DISSOLVING TABLETS OF CANDESARTAN CILEXITIL BY LYOPHILIZATION METHOD USING SKIMMED MILK

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ABSTRACT

Hypertension , congestive heart failure have become most serious and common problems in today's world. There are many dosage forms available but bed ridden, mentally ill and patients suffering from dysphagia suffers lots of problem in taking such conventional oral dosage forms .The present investigation was undertaken to formulate mouth dissolving tablet of Candesartan cilexitil which could solve most of the problems and provide good patient compliance with faster onset of action..To increase solubility and dissolution, solid dispersions of candesartan were prepared by lyophilization technique using TBA (tertiary butyl alcohol) as co-solvent .Skimmed milk was selected as carrier due to its taste masking , low cost and biocompatibility properties. Solid dispersions were prepared in ratios 1:3, 1:5, 1:7, 1:9. Solubility and *in vitro* studies showed better results for 1:5 (SD 2) and was selected for further studies .Drug polymer interaction was investigated by XRD and FTIR studies. Pre-compressional and post-compressional parameters were within prescribed limits and indicated good flow properties of powders.. To construct a statistical model, 3^2 full factorial design (FFD) was selected wherein camphor and crospovidone were selected as independent variables and disintegration time, friability were selected as dependent variables. Results indicated that optimized tablet provide disintegration time of 35 sec and friability 0.86%.

KEYWORDS: Candesartan cilexitil, Skimmed milk, Lyophilization, Camphor, Sublimation, mouth dissolving tablets.

INTRODUCTION

Mouth dissolving tablet is the innovative technology where dosage form disintegrate rapidly within matter of seconds without need of water[1]..Patient compliance, cost value and fast onset of action are the few requirements of any dosage form to occupy a big segment in market .Mouth dissolving tablets not only provide optimal patient compliance but is quite advantageous to the patients suffering from dysphagia, mental illness ,bronchitis, kinetosis (motion sickness), pediatrics and geriatrics.[2,3]

In the present study Candesartan cilexil was selected as model drug because of its low solubility and bioavailability. Candesartan cilexetil is a selective AT1 subtype angiotensin II receptor antagonist and candesartan acts by blocking the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues such as vascular smooth muscle and the adrenal gland. Candesartan is widely used in treatment of diseases like hypertension, heart failure, myocardial infarction and diabetic nephropathy.[4,5] Candesartan cilexetil is rapidly and completely bioactivated by ester hydrolysis during absorption from the gastrointestinal tract to Candesartan. Half life of Candesartan is 5.1-10.5 hrs and bioavailability of 15%.[6]

Skimmed milk was selected as carrier because of its drug compatibility and surface active properties. It also has property of modifying the crystallinity and non polarity of hydrophobic drug.[7,8]

Present investigation was undertaken to increase solubility , bioavailability of drug by making its solid dispersions by lyophilization technique using skimmed milk as carrier and to formulate it as mouth dissolving tablet by optimizing the variables (camphor &crospovidone) in 3^2 full factorial design.

MATERIALS AND METHODS

Materials

Candesartan cilexitil was obtained as gift sample from Ind Swift Pvt. Ltd., Dera Bassi, India..Skimmed milk of Nestle India Pvt Ltd was used. Camphor, microcrystaline cellulose, lactose were obtained from Loba chem. Pvt. Ltd,(Mumbai,India) .Magnesium stearate, talc and TBA(tertiary butyl alcohol) were obtained from signet Pvt. Ltd.,India.

Methods

Preparation of solid dispersion by Lyophilization method

Solid dispersions in skimmed milk were weighed in four ratios 1:3, 1:5, 1:7, 1:9.TBA was selected as co- solvent because it is an ideal freeze drying medium which is miscible with water and have high melting point (24ºC).Adding TBA to water results in formation of large needle shaped crystals with large surface area and porosity that can facilitate sublimation.

Candesartan (4 mg) was taken and dissolved in TBA (10 ml) and different ratios of skimmed milk were suspended in distilled water (5 ml). Above solutions were mixed to obtain homogenous carrier and drug solvent system. These solutions were frozen at -20ºC in a deep freezer for 1 hr.15 ml solution formed was taken into round bottom flask (RBF) and frozen for 2h followed with a condenser temperature of -78.5ºC .After complete freezing was achieved the RBF's were removed from freezing chamber, vacuum was applied and samples were subjected to lyophilization for 4h with vacuum of 0.02 mbar.In the end dried mass was formed in RBF which was placed in dessicator [9].

Solubility studies

Pure Candesartan cilexetil and solid dispersions equivalent to 10 mg of Candesartan cilexetil were added to 10 ml of phosphate buffer pH 6.8 in a 25 ml volumetric flasks. The volumetric flasks were capped properly and shaken at 37±2^{0}C in a temperature controlled water bath (Shaking water bath) for 48 h. Resultant samples containing undissolved solid dispersions suspended in the volumetric flask were filtered through Whatman filter paper (no. 41), suitably diluted with phosphate buffer pH 6.8 and analyzed by UV spectrophotometer at 256.4 nm.

***In vitro* drug release studies**

Accurately weighed solid dispersions equivalent to 10 mg of Candesartan cilexetil were added to 900 ml of dissolution medium (phosphate buffer pH 6.8) in USP II Paddle type apparatus and stirred at a speed of 50 rpm at 37±0.5^0 C. 5 ml aliquots were withdrawn at 5, 10, 15, 20, 25, 30 ,35, 40 ,45 minutes and replaced by 5 ml of fresh dissolution media (phosphate buffer, pH 6.8). The collected samples were analyzed after filtration and dilution at 256.4 nm using UV-visible spectrophotometer(Shimadzu 1700) against the blank. Drug release studies were carried out in triplicate. The dissolution studies of pure candesartan cilexetil were performed similarly.

Fourier Transform Infrared (FTIR) Spectroscopy

Fourier Transform Infrared (FTIR) spectra of pure drug, skimmed milk and solid dispersion (SD2) was recorded on IR spectrophotometer Bruker (alpha E). The scanning range was 4000 - 400 cm^{-1} and the resolution was 4 cm^{-1}.

Powder X-Ray Diffraction (XRD) Analysis

Powder X-Ray Diffraction (XRD) patterns of pure drug, skimmed milk and solid dispersion (SD2) were recorded using X-ray diffractrometer. Under the following conditions target Cuk_{α} monochromatized radiation, voltage 45KV, and current 40 mA at ambient temperature. The scanned range was 5^0-50^0.

Characterization of blends: To find out the flow property of powders. Bulk density, tapped density, Hausner's ratio, Compressibility index and angle of repose was also determined as shown in table 6.

PREPARATION OF MOUTH DISSOLVING TABLETS

Sublimation method Mouth dissolving tablets were compressed on single punch tablet machine .All raw materials were passed through 40 mesh screen prior to mixing. Camphor was used as sublimating agent which was subjected to vacuum drying at 50ºC.Minimum of 50 tablets weighing 100 mg were prepared.

Table 1: Preliminary trial batches of Candesartan cilexitil mouth dissolving tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
SD2 (Dose =4mg)	24	24	24	24	24	24	24	24	24
Camphor	2.5	5	7.5	-	-	-	-	-	5
Crospovidone	-	-	-	2.5	5	7.5	-	-	5
Mannitol	56.5	54	51.5	56.5	54	51.5	59	59	49
Talc	2	2	2	2	2	2	2	2	2
Lactose	2	2	2	2	2	2	2	2	2
Mag.Stearate	3	3	3	3	3	3	3	3	3
MCC	10	10	10	10	10	10	10	10	10
Total	100	100	100	100	100	100	100	100	100

EXPERIMENTAL DESIGN

A two factor, three level (3^2) FFD was used in the optimization of MDT's of Candesartan cilexitil. The study design involved the investigation of the effect of independent variables viz concentration of camphor (X_1) and concentration of crospovidone (X_2) on the dependent

variables such as disintegration time, and friability[10]. The combination of these trials is presented in Table 2

Table 2: Experimental plan of 3^2 full factorial design.

Formulation Code	Camphor Concentration (X_1)	Crospovidone Concentration(X_2)
F-1	-1	-1
F-2	-1	0
F-3	-1	+1
F-4	0	-1
F-5	0	0
F-6	0	+1
F-7	+1	-1
F-8	+1	0
F-9	+1	+1

CODED VALUES	ACTUAL VALUES
-1	2.5
0	5
1	7.5

The levels of the factors studied were chosen on the basis of results of preliminary studies The responses were analyzed using Design Expert Trial Version 9.0.4 software. Statistical models were generated for each response parameter. The models were tested for significance. The optimum MDT having highest desirability was prepared with best concentration of Camphor and Crospovidone. The amount was suggested by the software.

A statistical model, $Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1X_1 + b_{22}X_2X_2$, incorporating interactive and polynomial terms was used to evaluate the responses; where Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The term (X_1X_2) indicates the interaction between two factors. The polynomial terms (X_1X_1 and X_2X_2) are included to investigate nonlinearity.

CHARACTERIZATION OF MOUTH DISSOLVING TABLETS.

General Appearance

This includes tablets size, shape, colour, presence or absence of an odour, surface texture, physical flaws, legibility .

Tablet Thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by suing filling equipment. Ten tablets were taken and their thickness was recorded using micrometer (Mityato, Japan).

Uniformity of Weight

All the prepared batches of MDT were subjected to weight variation test, as per USP. Twenty tablets were taken and weighted individually, their average weight was calculated and compared with the individual tablet weight for any change produced.

Table 3: Weight Variation Limits for Tablets as per USP

Average of Tablets (mg)	Maximum % difference allowed
130 or less	10
130-324	7.5
More than 324	5

Tablet Hardness

Hardness of the MDT of each batch was determined using Pfizer hardness tester. It tells us about the chipping ,abrasion or breakage of tablets under conditions of storage and handling.

Friability

Friability of the tablets was determined using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm for 4 minutes and dropping the tablets at a height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (%F) is determined by the formula.

$$\%F = (1 - \frac{W_o}{W}) \times 100$$

Where, W_0 is initial weight of the tablets before the test and W is the weight of the tablets after test.

Disintegration Test

Modified method: Disintegration of mouth dissolving tablets is achieved in the mouth owing to the action of saliva, however amount of saliva in the mouth is limited and no tablet

disintegration test was found in USP and IP to simulate *in vivo* conditions. A modified method was used to determine disintegration time of the tablets.

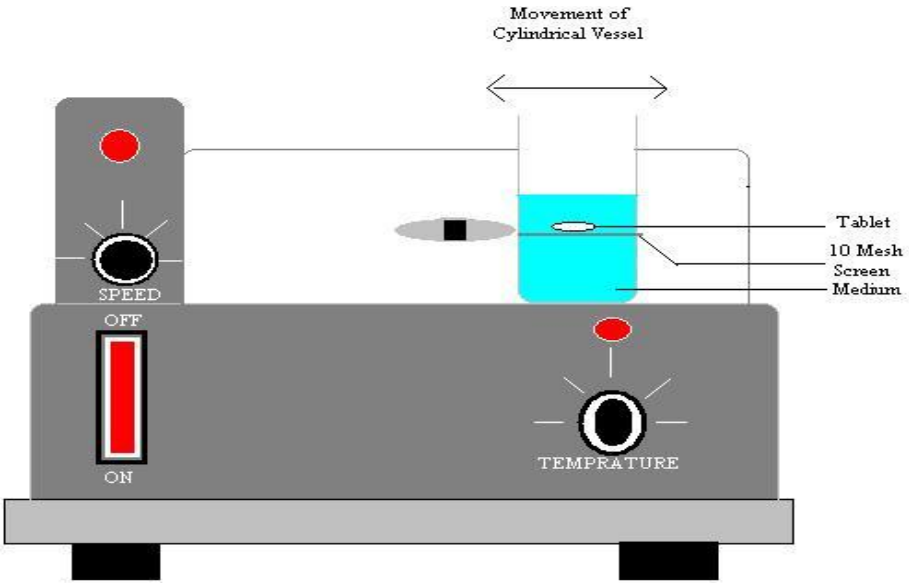

Fig 1:Modified device used to determine disintegration time

(i)In phosphate buffer 6.8

A cylindrical vessel was used in which 10-meshscreen was placed in such way that only 2 ml of disintegrating or dissolution medium would be placed below the sieve. To determine disintegration time, 6 ml of phosphate buffer (pH 6.8), was placed inside the vessel in such way that 2 ml of the media was below the sieve and 4 ml above the sieve. Tablet was placed on the sieve and the whole assembly was then placed on a shaker. The time at which all the particles pass through the sieve was taken as a disintegration time of the tablet. Six tablets were chosen randomly from the composite samples and the average value was determined.[11] Same experiment was repeated by taking 4ml of saliva of healthy volunteer

Wetting Time

The method was followed to measure tablet wetting time. A piece of tissue paper (10cm X 10 cm) folded twice was placed in a small petri dish (ID = 65 cm) containing 10 ml of phosphate buffer (pH 6.8), A tablet was put on the paper, and the time for the complete wetting was measured. Three trials for each batch were performed and the standard deviation was also determined[12].

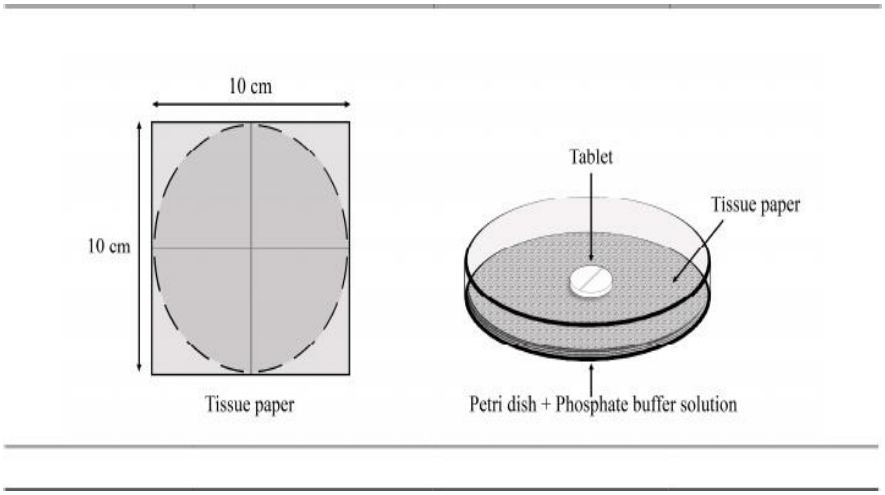

Fig. 2: Schematic ilustration of determination of tablet wetting time

In vitro Dispersion Time

In vitro dispersion time was measured by dropping a tablet in a glass cylinder containing 6 ml of phosphate buffer (pH 6.8). Three tablets from each formulation were randomly selected and *in vitro* dispersion time was calculated.

In vitro Dissolution Study

Dissolution study was carried out manually as no pharmacopoeia detail is mentioned regarding dissolution of mouth dissolving tablets. 25 ml beaker was placed on mechanical stirrer containing 6 ml phosphate buffer (pH 6.8) as dissolution medium maintained at 37 ± 0.5 ^{O}C. The medium was stirred as 75 rpm. Aliquots 1 ml dissolution medium were withdrawn at 2,4,6,8,10,15,20 25 ,30 min time intervals and same amount was replaced with the dissolution medium. The collected samples were analysed after filtration at 256.4 nm using UV spectrophotometer against the blank. Drug release studies were carried out in triplicate and cumulative percentage drug release was calculated.

Drug Content Uniformity

For the content uniformity test, ten tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to 4 mg of Candesartan cilexetil was extracted into phosphate buffer solution pH 6.8 and liquid was filtered through whatman filter paper. The Candesartan cilexetil content was determined by measuring the absorbance at 256.4nm (Shimadzu-1700 UV-Visible spectrophotometer) after appropriate dilution with phosphate buffer solution pH 6.8. The drug content was determined using standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

STABILITY STUDIES[13-14]

Temperature dependent stability studies

Accelerated stability studies were checked as per the ICH guidelines at 40±2ºC and 75±5% RH for three months.Optimized tablets were kept in wide mouthed air tight glass container. The tablets were withdrawn after a period of 15 days and analyzed for physical characterization and drug content spectrophotometrically at 256.4 nm Among several methods investigated Moore and Flanner independent mathematical approach was selected for similarity factor(*f2*)

$$f_2 = 50 \bullet \log \{[1+1/n\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \bullet 100$$

Where R_t and T_t are the cumulative percentage dissolved at each of the selected n time points of the reference and test product respectively.

When the two profiles are identical, *f2*=100. An average difference of 10% at all measured time point's results in a *f2* value of 50. FDA has set a public standard of *f2* value between 50 - 100 indicate similarity between two dissolution profiles.

RESULTS AND DISCUSSIONS

SOLUBILITY STUDIES

Solubility data of Candesartan cilexetil and solid dispersions in phosphate buffer pH 6.8 at 37±2^{0}C are shown in table 4 respectively and graph is represented in figure 3.

Table 4: Solubility Data of Candesartan cilexetil and solid dispersions in phosphate buffer (pH 6.8) at 37 ± 2^0 C

Formulation Number	Solubility (µg/ml)
Pure drug	24±0.001
SD1	212±0.006
SD2	530±0.006
SD3	304±0.008
SD4	405±0.003

* Values represent the mean ±SD of three experiments.

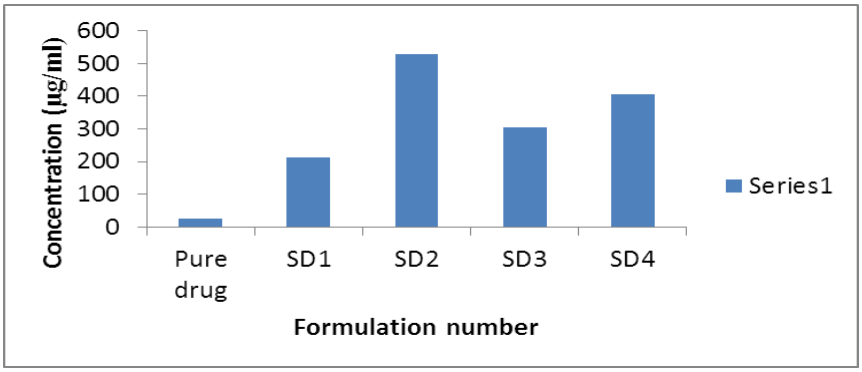

Figure 3: Solubility plot of Candesartan cilexetil and solid dispersion at 37 ± 2^0C

DISSOLUTION RELEASE PROFILE

The dissolution profile of pure drug and solid dispersion were carried out in phosphate buffer (pH 6.8). Dissolution release values are shown in table 5. From the data, it is evident that the onset of dissolution of pure Candesartan cilexetil was very low. The dissolution release from pure Candesartan cilexetil was only 16.4% in 45 minutes. Therefore, this release suggested a strong need to enhance the dissolution of Candesartan cilexetil. The presence of skimmed milk increases the dissolution of Candesartan cilexetil from the solid dispersion, which increases the dissolution rate as shown in figure 4. This is clear from the dissolution studies that the solid dispersion (1:5) of Candesartan cilexetil:Skimmed milk gives fastest dissolution of drug as compared to other formulation. The release profile showed 2 different phases of drug release. An initial rapid phase followed by a slower one. These results could be attributed to the general phenomenon of particle size reduction during the dissolution process medium by Skimmed milk. Solid dispersion technique has improved the dissolution rate of Candesartan cilexetil to greater extent.

Table 5: Dissolution Release Profile of Candesartan cilexetil and from solid dispersion Formulations

Time(min)	Pure Drug	SD1	SD2	SD3	SD4
0	0±0	0±0	0±0	0±0	0±0
5	1.154±0.02	38.283±1.65	52.743±1.54	51.456±1.07	50.221±0.28
10	2.621±0.01	44.544±1.33	54.765±1.55	54.334±3.31	52.543±0.17
15	4.802±0.15	48.721±1.45	63.732±0.58	56.911±0.33	55.022±0.31
20	6.231±0.13	55.422±1.32	68.654±0.24	65.755±0.12	64.124±0.15
25	9.214±0.16	64.754±0.28	79.381±0.15	71.722±0.12	69.055±0.12
30	10.231±0.15	68.544±0.72	82.453±0.16	74.821±0.13	72.234±0.23
35	13.327±0.03	72.654±0.23	88.413±0.22	77.561±0.15	75.013±0.32
40	15.211±0.03	78.234±023	91.345±0.32	78.546±0.12	78.244±0.15
45	16.402±0.16	81.456±0.33	97.154±0.31	82.445±0.14	82.533±0.16

* Values represent the mean ±SD of three experiments

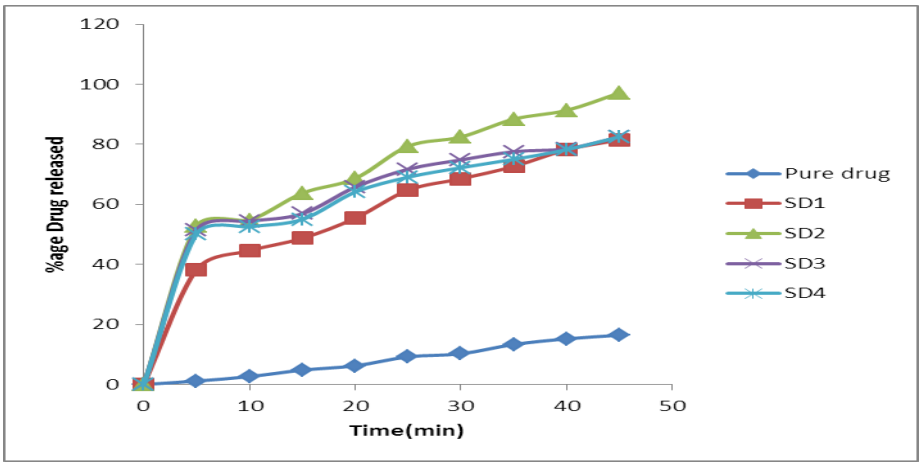

Figure 4: Percent Release of Candesartan cilexetil and from solid dispersions

FT-IR STUDIES

The FTIR studies were performed to check the possible interaction of the drug with the polymer. The spectrum of pure Candesartan cilexitil depict the characteristic peaks at peaks at 2938.64 cm^{-1} corresponding to CH_3 (alkane) strectching, at 1710.77 cm^{-1} corresponding to C=O (ester) , at 1611.69 cm^{-1} corresponding to C-N stretching, at 1274.58 cm^{-1} corresponding to C-O stretch, at 1115.42 cm^{-1} corresponding to C-N (aliphatic amine), at 691.28cm^{-1} corresponding to C-H out of plane bending.

While FT-IR of Skimmed milk shows peaks at 3373.99 cm^{-1} corresponding to O-H bond stretching (α-cellulose),at 2921.96 cm^{-1} corresponding characteristic absorption of polysaccharides, at 1648.25 cm^{-1} shows presence of proteins in chemical structure, at 1379.30 cm^{-1} corresponding to NH_2 bonding (tertiary amides),at 1152.51cm^{-1} and 1135.49cm^{-1} corresponding to C-O stretching, at 1026.92 cm^{-1} corresponding to starch content (glycogen) in the sample, at 903.87cm^{-1},753.36 cm^{-1}corresponding to carbohydrates .

The presence or absence of characteristic peak associated with specific structural groups of the drug molecule and skimmed milk were noted. The FT-IR spectra of dispersions showed almost all the characteristic peaks of the drug and skimmed milk, without affecting their peak position which indicated lack of interaction between the drug and the polymer.

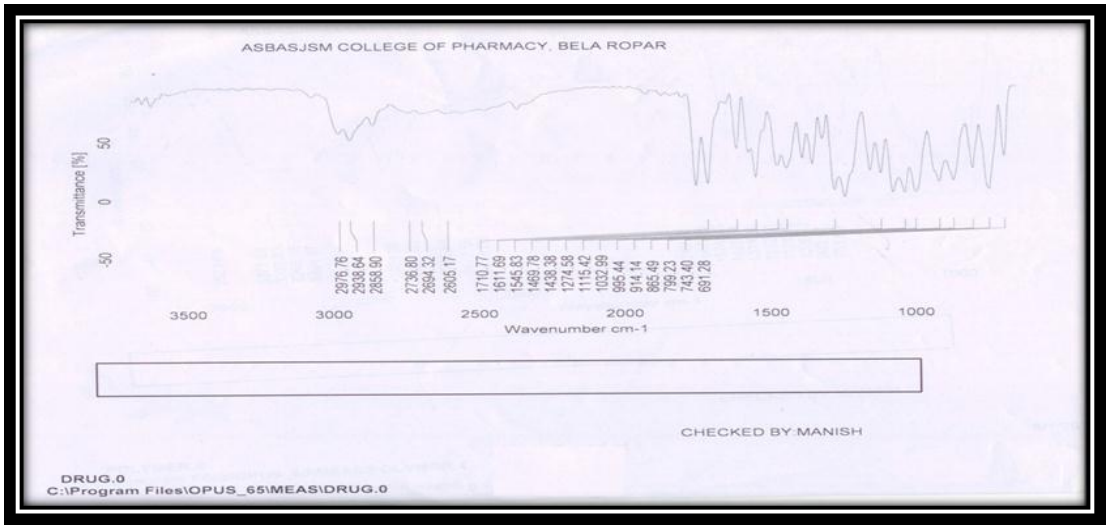

Fig 5: IR spectra of Candesartan cilexitil

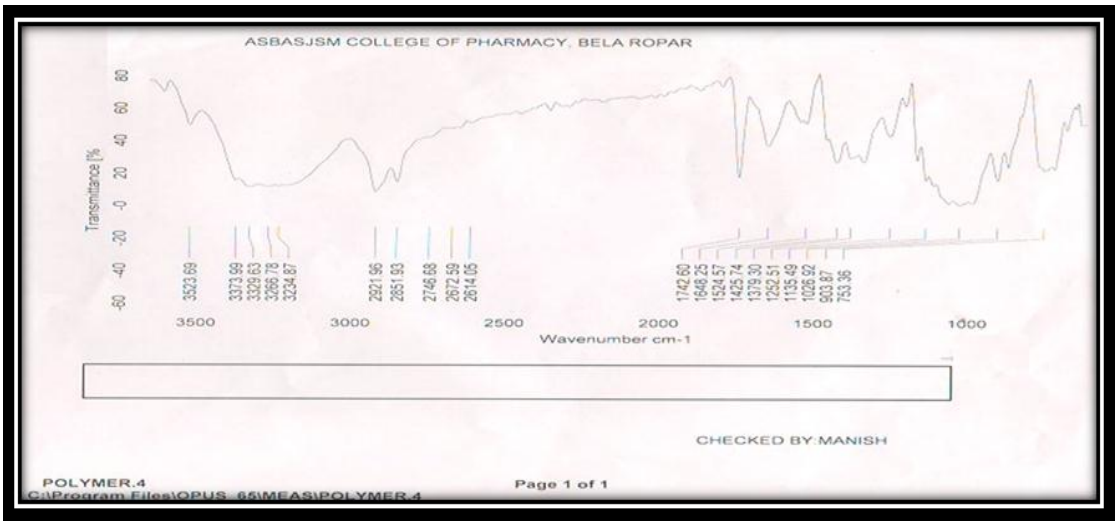

Fig 6 :IR Spectra of skimmed milk (polymer)

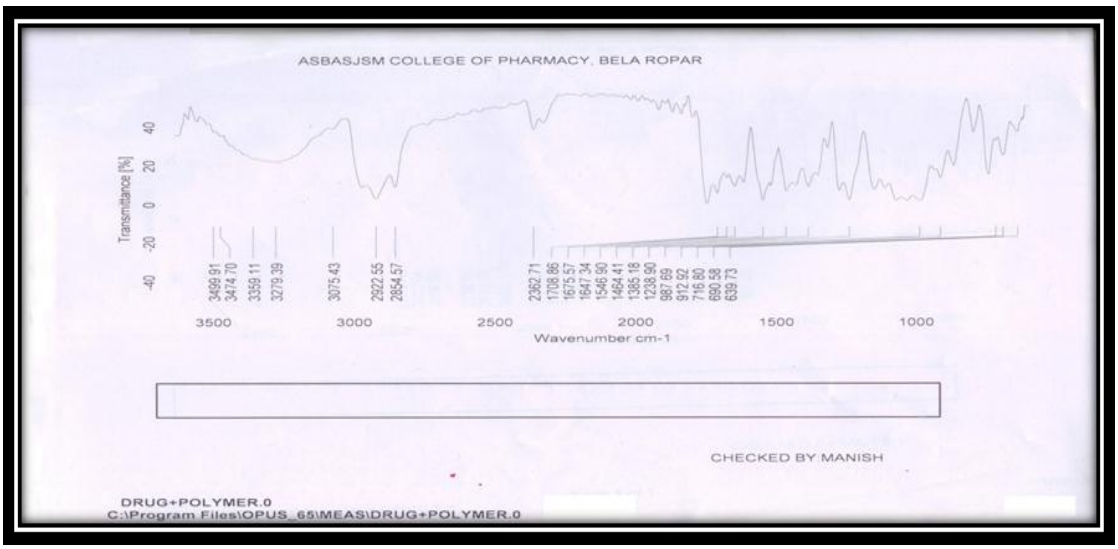

Fig 7: IR Spectra of solid dispersion (SD2)

XRD ANALYSIS

Pure Drug: In the X-ray diffractrogram of Candesartan cilexetil, sharp peaks at diffraction angle (2θ) of 9.8^0, 17.17^0 and 23. 2^0 indicate the presence of crystalline drug as shown in fig 8.

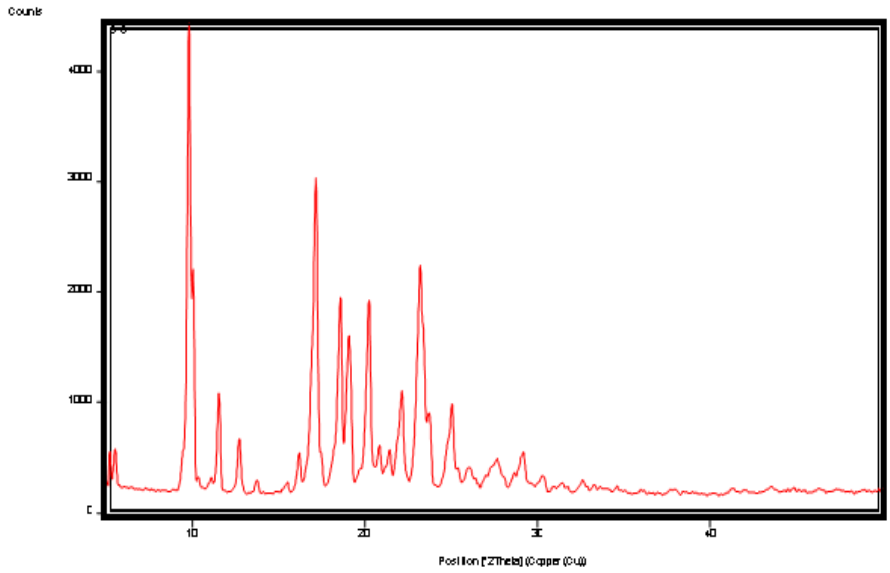

Fig 8: XRD Spectra of: (A) Candesartan cilexitil

Skimmed milk: : XRD pattern of Skimmed milk showed one characteristic peaks of high intensity at diffraction angle 2θ of 17.27º which shows amorphous nature of skimmed milk. as shown in fig 9.

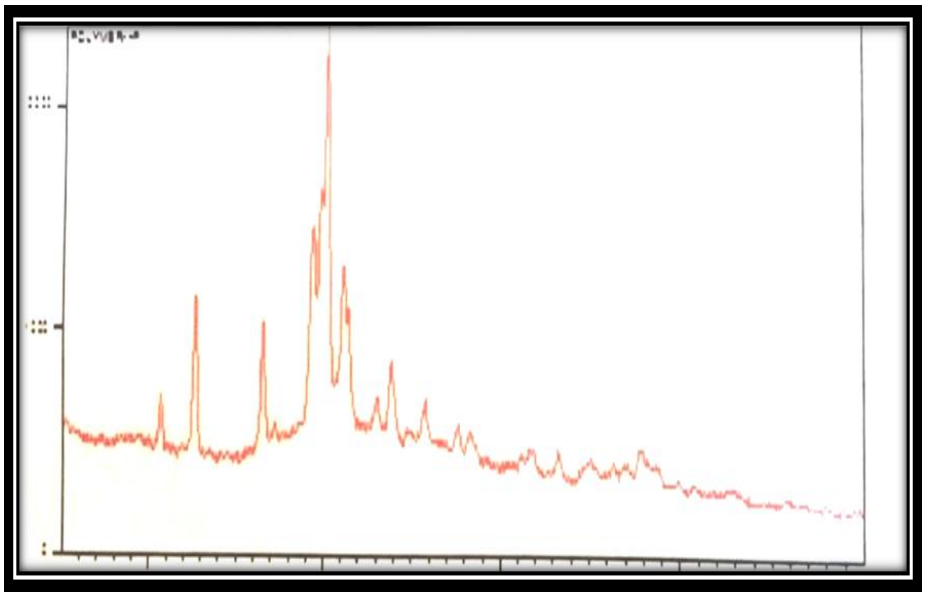

Fig 9: XRD Spectra of: (B) Skimmed milk

Solid dispersion: Solid dispersion shows peaks at 9.9239º, , 17.2948º .The XRD of solid dispersion exhibits peaks less than the sum of the number of peaks of Candesartan and Skimmed milk in their pure form.This suggests that crystallinity of the drug and polymer is reduced in solid dispersion. Decrease in crystallinity of the drug and polymer contribute to enhancement of dissolution of drug,shown in fig 10.

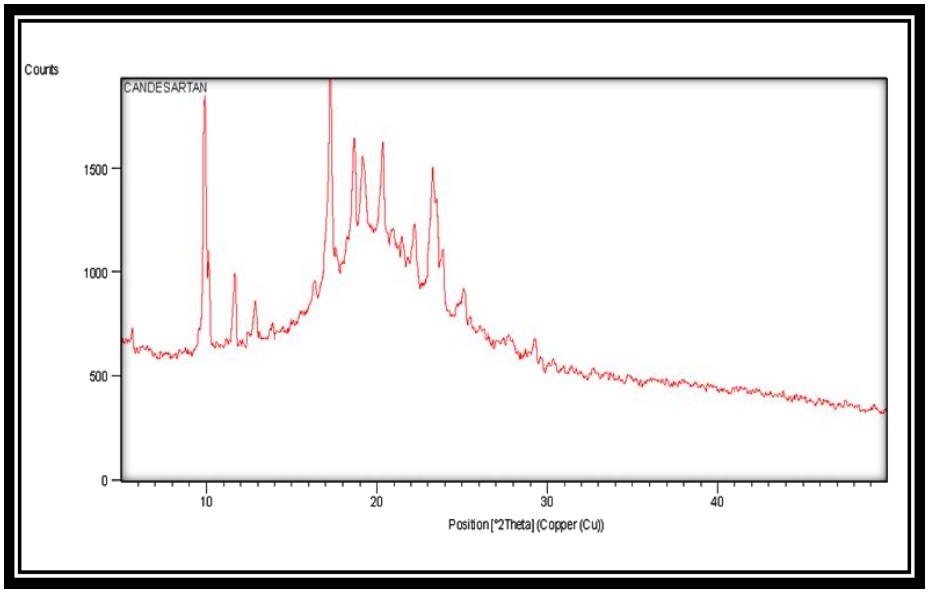

Fig 10: XRD Spectra of Solid dispersion

CHARACTERIZATION OF BLENDS

Table 6: Characterization of blends (Pre-compressional parameters)

Parameters Formulation	Bulk Density (g/cc)	Tapped Density (g/cc)	Hausners Ratio	Compressibility Index (%)	Angle of Repose(º)
F- 1	0.55±0.008	0.63±0.006	1.15±0.030	12.53±2.18	25.265±1.70
F - 2	0.55±0.003	0.68±0.018	1.23±0.040	19.09±1.82	22.521±1.30
F- 3	0.51±0.002	0.71±0.008	1.39±0.010	28.14±1.42	24.533±1.49
F-4	0.53±0.006	0.69±0.039	1.28±0.066	22.02±4.08	23.408±1.67
F-5	0.59±0.007	0.67±0.004	1.13±0.021	12.07±1.63	24.624±1.36
F-6	0.59±0.002	0.70±0.005	1.19±0.08	15.84±0.26	22.163±1.41
F-7	0.59±0.002	0.68±0.017	1.15±0.026	12.42±0.81	25.450±1.50
F-8	0.66±0.006	0.63±0.021	1.12±0.028	12.006±0.71	28.121±1.21
F-9	0.60±0.002	0.68±0.011	1.13±0.012	11.70±0.43	25.117±1.39

* Values represent the mean ±SD of three experiments

Table 7: Characterization of mouth dissolving tablets (Post-compressional parameters)

Parameters / Formulations	Thickness (mm)	Weight variation(mg)	Friability (%)	Hardness (kg/cm^2)
F-1	2.510±0.021	97.9±3.176	0.89±0.046	2.9±0.133
F-2	2.258±0.034	99.2±2.923	0.85±0.045	2.7±0.113
F-3	2.319±0.008	101.6±3.765	0.82±0.060	2.8±0.109
F-4	2.385±0.016	96.4±3.874	0.91±0.057	2.5±0.165
F-5	2.609±0.339	100.4±4.246	0.89±0.072	2.5±0.165
F-6	2.523±0.028	101.9±3.876	0.85±0.029	2.6±0.146
F-7	2.342±0.019	99.4±2.793	0.98±0.037	2.7±0.155
F-8	2.415±0.016	97.8±2.686	0.97±0.048	2.4±0.136
F-9	2.634±0.022	98.6±2.952	0.80±0.058	2.5±0.154

* Values represent the mean ±SD of three experiments

Table 8: Characterization of mouth dissolving tablets

Formulation code	Disintegration time(sec)		Wetting time (sec)	Dispersion Time (sec)	Drug content (%)
	Buffer (pH 6.8)	Saliva			
F-1	32.00±5.56	40.02±3.05	58.33±5.68	82.33±6.42	98.32±0.79
F-2	25.02±2.08	38.06±2.31	54.33±3.21	80.33±5.13	97.47±0.59
F-3	21.02±1.52	28.12±1.34	50.66±4.04	62.33±4.04	97.68±0.65
F-4	42.01±2.51	39.31±1.11	60.66±2.08	75.66±3.51	97.90±0.72
F-5	38.04±1.52	35.54±2.32	58.00±1.00	64.66±2.51	98.54±0.81
F-6	30.00±1.93	29.02±1.52	51.16±1.85	59.24±2.97	98.11±1.23
F-7	54.01±1.35	50.54±2.22	72.25±1.63	102.42±5.37	98.54±0.81
F-8	52.00±1.21	46.32±1.21	68.21±1.08	94.58±2.76	98.86±0.92
F-9	18.04±0.92	21.12±1.23	22.16±0.04	40.33±2.15	99.40±1.81

*Values represent the mean ±SD of three experiments

Table 9: *In Vitro* release of Candesartan mouth dissolving tablet (F1-F-9)

Time (min)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
2	63.149±2.07	65.878±0.29	68.217±0.30	54.573±2.98	58.082±1.72	61.980±1.74	44.303±0.55	49.624±1.76	70.945±0.55
4	66.268±.531	67.827±0.17	69.386±0.17	56.912±2.99	60.421±1.73	63.149±1.75	47.032±0.30	52.963±3.06	73.674±0.30
6	68.607±0.36	70.556±0.3	72.505±0.30	59.641±0.44	63.929±0.581	65.878±2.64	50.540±0.01	54.082±1.78	75.233±0.01
8	71.725±0.16	73.284±0.17	75.233±0.17	62.759±0.37	67.647±0.28	69.386±2.40	53.659±0.01	55.810±1.88	78.352±0.01
10	73.674±0.164	75.623±0.04	77.962±0.05	65.878±0.31	70.556±0.16	72.115±1.42	56.387±0.01	58.539±0.29	81.081±0.01
15	76.403±0.16	78.352±0.46	80.691±0.30	68.996±0.17	73.284±0.16	74.844±0.68	58.726±1.76	62.047±0.74	83.419±1.76
20	79.521±0.16	81.470±0.07	83.809±0.30	72.115±0.20	76.013±0.28	77.182±0.68	63.014±0.35	65.556±0.02	86.148±0.35
25	82.640±0.16	84.199±0.30	86.538±0.18	75.623±0.37	79.132±0.08	80.301±1.22	65.743±0.17	68.844±0.397	89.267±0.17
30	84.979±0.16	86.148±0.37	90.046±0.18	80.691±0.31	81.860±0.33	83.419±0.91	69.251±0.17	72.132±0.57	91.995±0.17

* Values represent the mean ±SD of three experiments

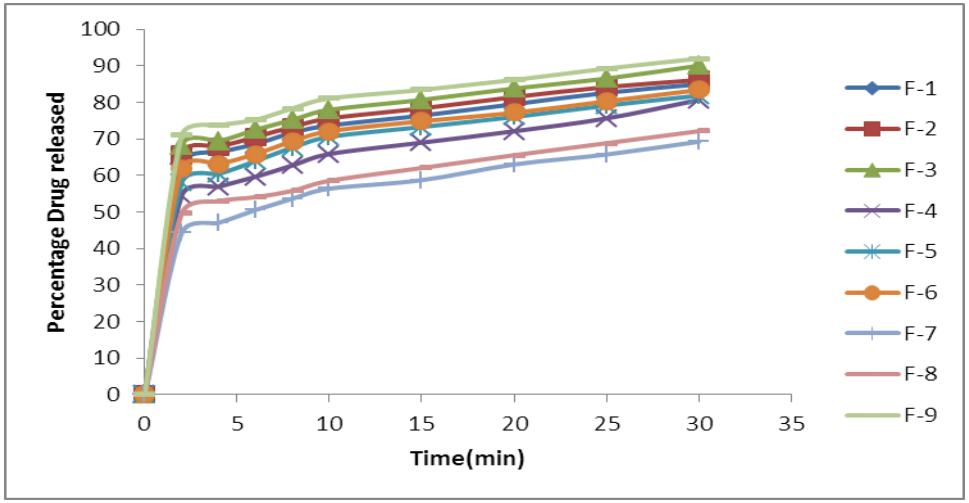

Fig 11 :*In vitro* release of mouth dissolving tablets of Candesartan cilexitil(F1-F9)

OPTIMIZATION

Factorial designs

Table 10: Factorial design layout for camphor+ crospovidone

BATCH CODE	Variable Levels in Coded Form		D.T.	Friability
	X_1(camphor)	X_2(crospovidone)	Y_1(sec)	Y_2 (%)
F-1	-1	-1	52	0.94
F-2	-1	0	50	0.80
F-3	-1	+1	40	0.75
F-4	0	-1	50	0.98
F-5	0	0	44	0.88
F-6	0	+1	35	0.82
F-7	+1	-1	37	0.98
F-8	+1	0	26	0.90
F-9	+1	+1	18	0.85

Coded Values	Actual Values	
	X_1 (camphor)	X_2 (crospovidone)
-1	2.5	2.5
0	5	5
+1	7.5	7.5

Table 11: Optimization of mouth dissolving tablet

CONSTRAINTS			
NAME	GOAL	Lower Limit	Upper Limit
Camphor	Is in range	-1	+1
Crospovidone	Is in range	-1	+1
D.T. (sec)	Is target =35	18	52
Friability (%)	Is target =0.86	0.75	0.98

Table 12: Summary of results of regression analysis

Response	B_0	B_1	B_2	B_{12}	B_{11}	B_{22}
D.T.	43.89	-10.17	-7.67	-1.75	-5.83	-1.33
p value		0.0009	0.0020	0.1538	0.208	0.3816
%Friability	0.88	0.040	-0.080	0.015	-0.023	0.027
p value		0.0028	0.0004	0.0679	0.0542	0.389

$$D.T. = 43.89 - 10.17X_1 - 7.67X_2 - 1.75X_1X_2 - 5.83X_1X_1 - 1.33X_2X_2 \quad ...eqn\ (1)$$

$$\% \text{ Friability} = 0.88 + 0.040X_1 - 0.080X_2 + 0.015X_1X_2 - 0.023X_1X_1 - +0.027X_2X_2$$

Table 13: Results of analysis of variance

Response		df	Sum of square	Mean square	F	R^2
D.T.	Model	5	1056.69	211.34	62.19	0.9904
	Residual	3	10.19	3.40		
% Friability	Model	5	0.051	0.010	89.55	0.9933
	Residual	3	3.44	1.148		

Response surface plots

Response surface plots were generated for each response to study the effect of each factor and the behaviour of the system.

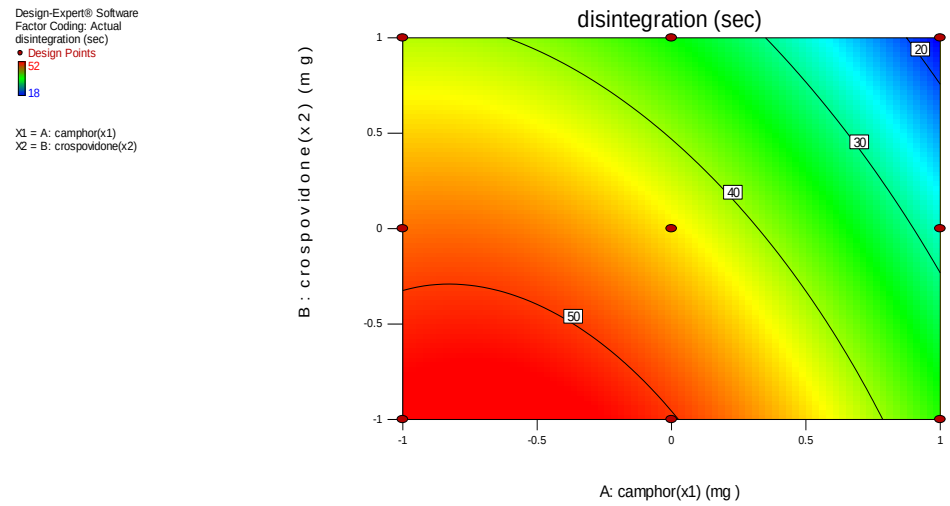

Fig 12: Contour plot for disintegration time

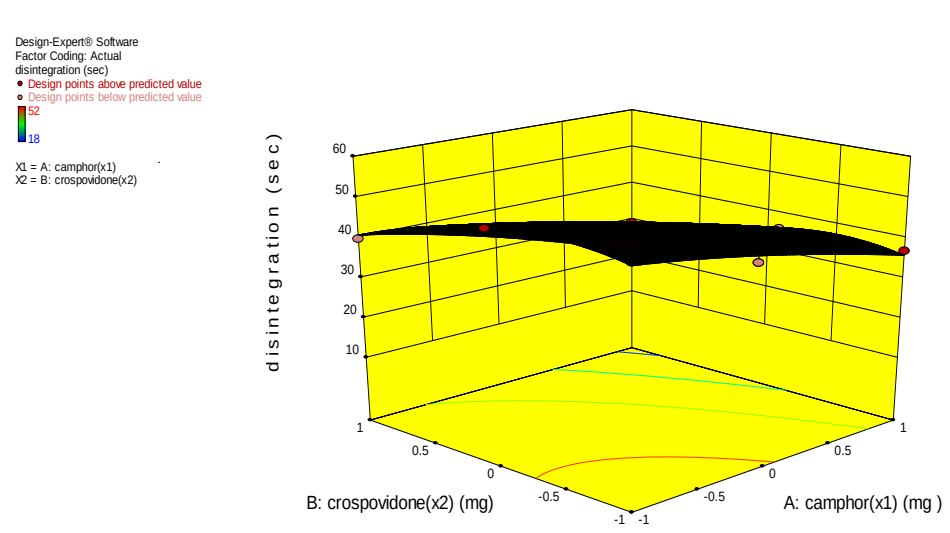

Figure 13: Response surface plot for disintegration time

It was observed that disintegration time was dependent on both factors. A linear decrease in the disintegration time was observed with an increase in the levels of both factors camphor and crospovidone enhances faster disintegration.

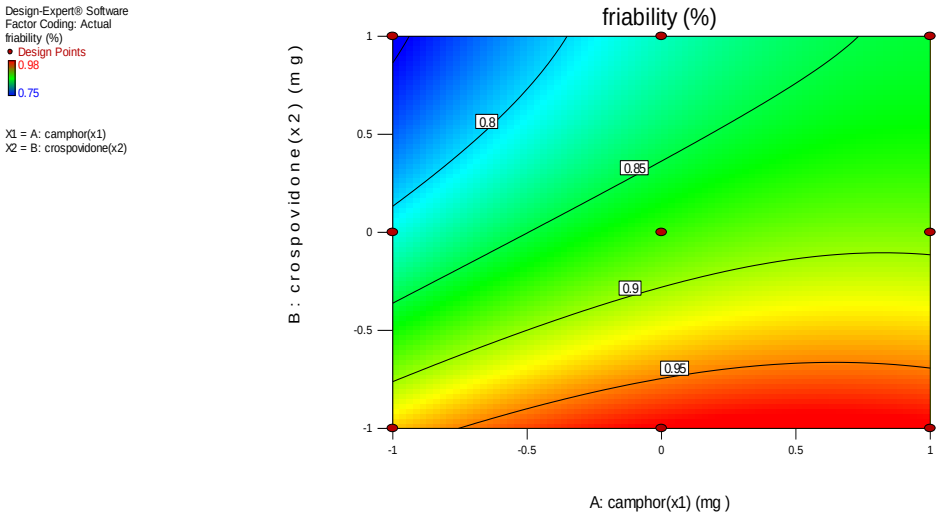

Fig 14: Contour plot for friability

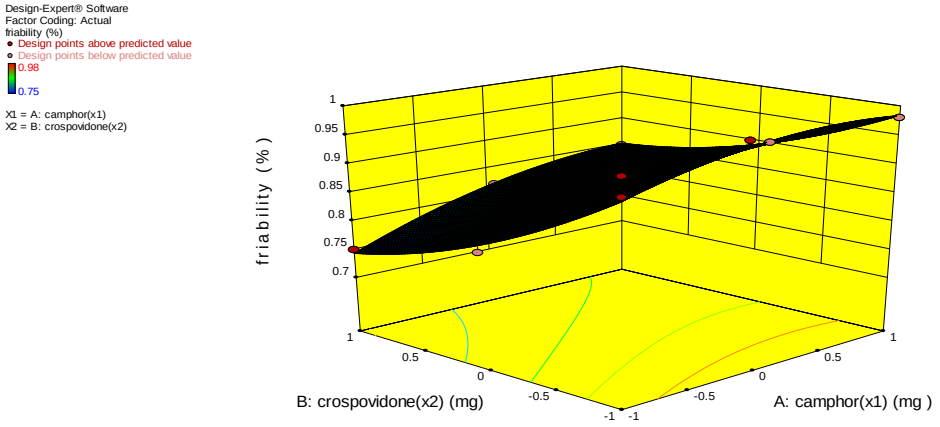

Fig 15: Response surface plot for friability

Response surface plots for percent friability clear that both the factors had influence on percent friability of the tablets. An increase percent friability observed with increasing concentration of camphor and decrease in percentage friability observed with increase in concentration of Crospovidone.Thus optimum values of friability were selected keeping in view this trend.

Optimum formulation

Using software Design Expert 9.0.4 the disintegration time, percentage friability were 35 sec, 0.86% respectively and desirability was 1

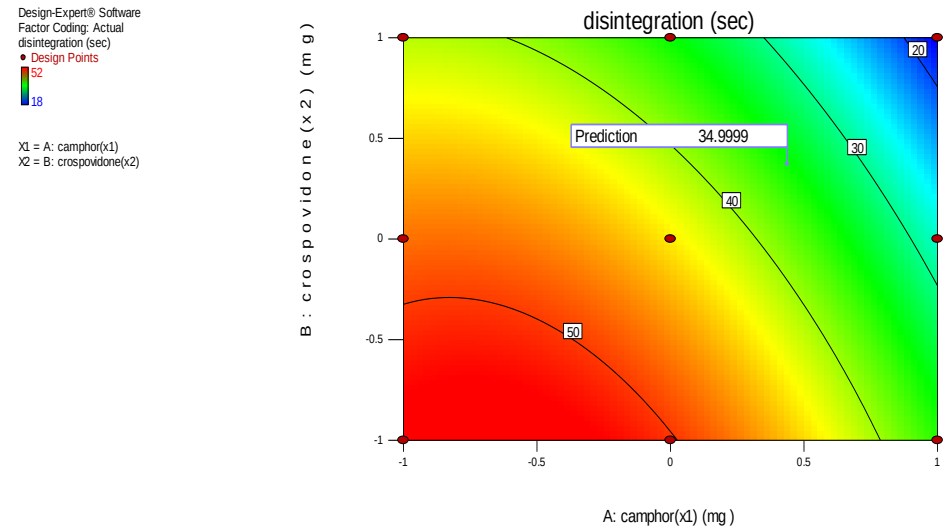

Fig 16 Response surface of optimized formulation (disintegration)

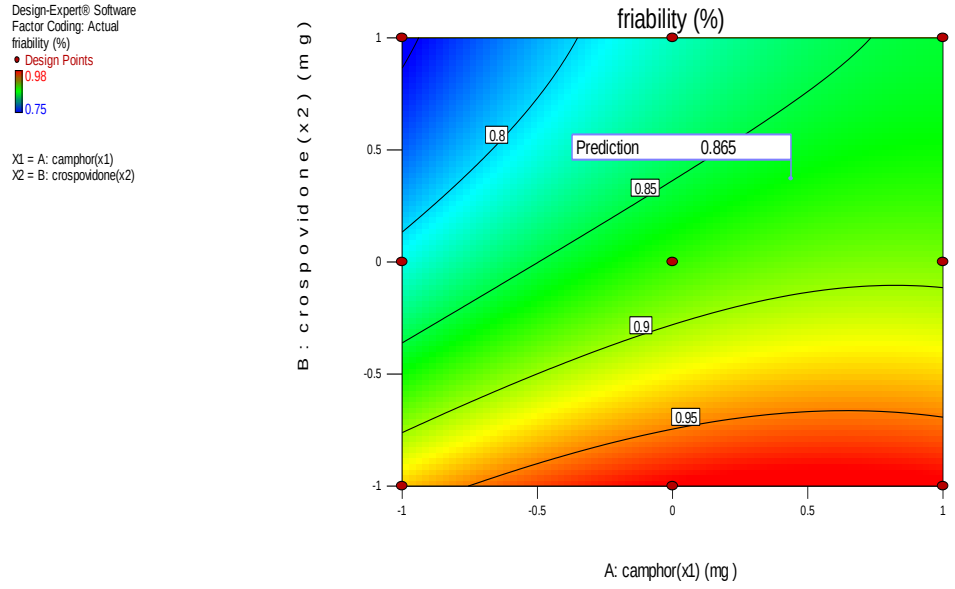

Fig 17:Response surface of optimized formulation (friability)

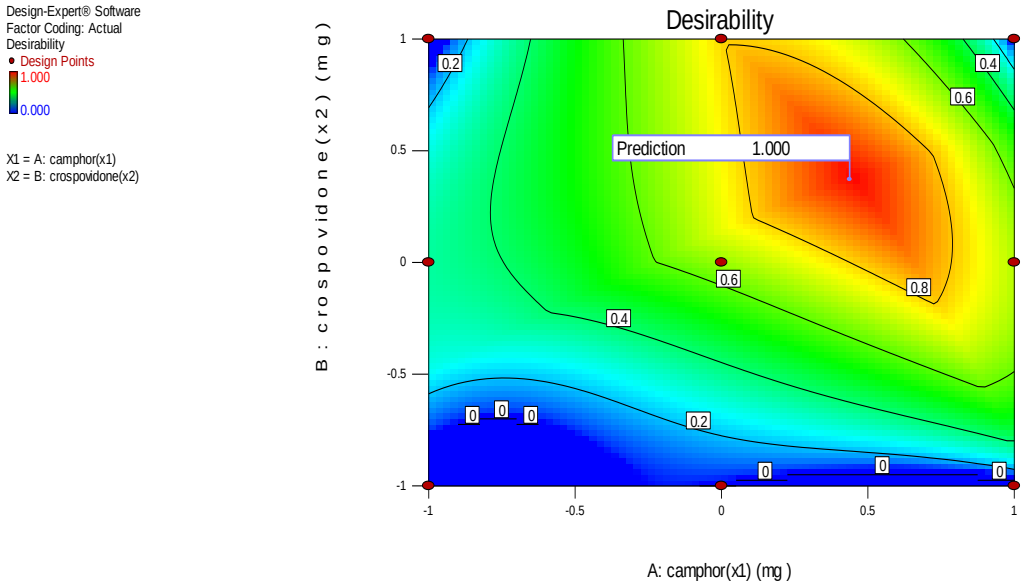

Fig 18:Response surface of optimized formulations (desirability)

Optimum formulation for mouth dissolving tablets of Candesartan cilexitil

The optimized formulation was prepared with best concentration of camphor and crospovidone. The amount was suggested by the software design expert 9.0.4. The optimized tablets were prepared and characterized for their physiochemical properties.

Table 14: SOLUTION

Camphor X_1	crospovidone X_2	D.T. (sec)	Friability (%)	Desirability
0.438 (6.0 mg)	0.372 (5.9 mg)	35	0.86	1.00

EVALUATION PARAMETERS OF OPTIMIZED TABLETS

Table 15: Optimized Candesartan cilexitil formulation

Ingredients	Quantity per tablet (mg)
Solid dispersion(1:5)	24
Camphor	6.0
Crospovidone	5.9
Avicel PH101	10
Mannitol	47.1
Lactose	2.0
Talc	2.0
Magnesium Stearate	3.0

COMPARISION WITH MARKETED TABLETS

Table 16: Selected optimized formulation and marketed formulation

Parameters	Selected formulation	Marketed formulation(candesar)
Weight (mg)	98.8±.57	99.2±1.21
Hardness (kg/cm^2)	2.4±0.3	3.4±0.52
Friability (%)	0.86±0.013	0.833±0.051
Disintegration time	35±0.00 (sec)	26.34±3.81 (mins.)
Drug content (%)	99.50±0.98	98.87±1.34

* Values represent the mean ±SD of three experiments

Table 17: Percentage drug released data

Time (min)	Percentage drug released of Optimized Formulation	Percentage drug released of Marketed Formulation(candesar)
2	70.92±.027	07.15±0.12
4	73.65±.033	08.83±0.23
6	75.21±.031	10.33±0.37
8	78.32±0.046	12.02±0.48
10	81.18±0.13	13.32±0.56
15	83.41±1.74	15.24±0.74
20	85.14±0.32	17.42±0.28
25	89.26±0.17	20.13±1.01
30	91.99±0.17	23.33±1.27

* Values represent the mean ±SD of three experiments

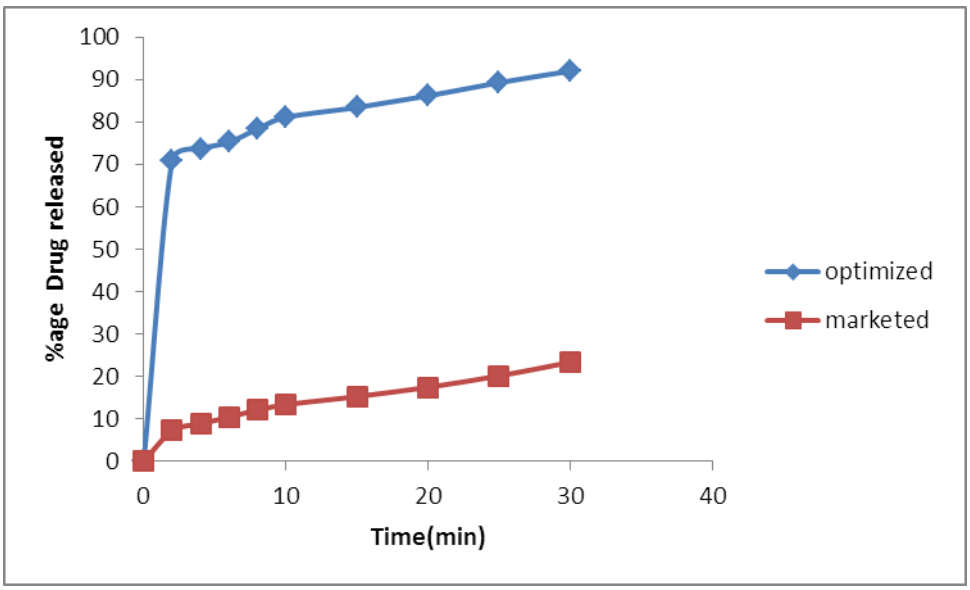

Fig 19: Percentege drug released curve of optimized Candesartan cilexetil and marketed tablet (Candesar)

STABILITY STUDIES

Selected formulation showed no signification variation in all the parameters under the test period at different conditions i.e. $40^{\pm}2^{0}$C and RH 75±5%. The results are shown in table 18.

Table 18: Effect of storage conditions on optimized tablet

Days	Weight (mg)	Hardness (kg/cm^2)	Friability (%)	Disintegration Time(s)	Drug Content(%)
0	98.80±.57	2.5±0.3	0.86±0.01	35±0.00	99.50±0.98
15	98.11±2.074	2.5±1.23	0.86±0.18	35±0.08	99.24±2.81
30	98.03±3.13	2.5±1.34	0.86±0.36	35±2.32	99.21±4.04
45	98.78±1.79	2.4±1.57	0.86±0.53	35±2.44	99.13±2.34
60	99.03±1.82	2.4±1.18	0.86±0.19	36±3.12	98.99±2.93
75	99.22±2.36	2.3±1.09	0.87±0.06	36±3.44	98.90±2.0
90	99.45±2.22	2.3±1.02	0.87±0.26	36±3.50	98.79±1.85

* Values represent the mean ±SD of three experiments

Table 19: Comparison of drug release data before and after storage

Time (mins.)	Cumulative Percent Drug Released ± S.D.	
	Initial	After 3 months
2	70.92±.027	69.82±0.014
4	73.65±.033	72.13±0.041
6	75.21±.031	74.62±0.015
8	78.32±0.046	77.62±0.033
10	81.18±0.13	80.32±0.032

* Values represent the mean ±SD of three experiments

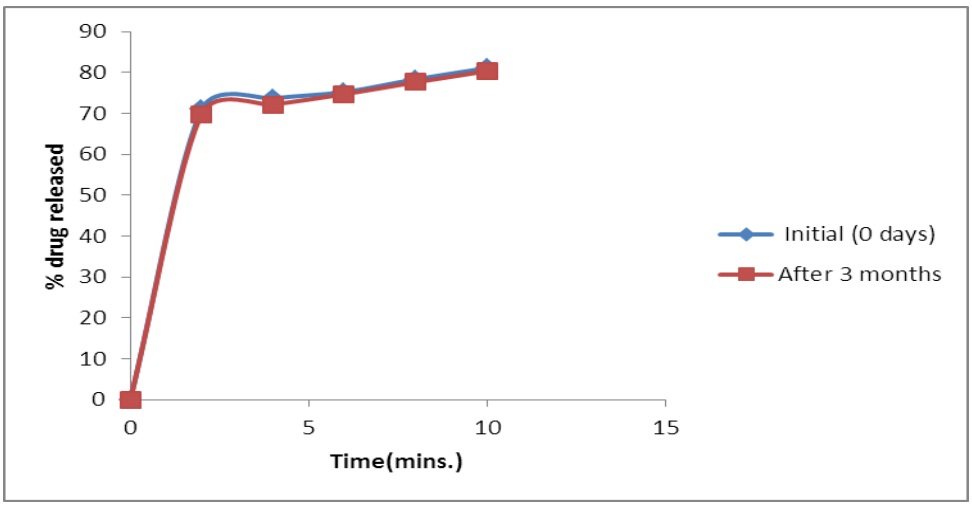

Fig 20: Comparison of drug release data before and after storage

The similarity factor was calculated for the comparison of the dissolution profile before and after stability studies. The f_2 value was found to be more than 50 (i.e. 80.81) thereby indicating a close similarity between both the dissolution profiles.

Hence, the result of the stability studies confirmed that the developed formulation is very stable.

CONCLUSION

The results of experimental study confirmed that the factors X1(Camphor) and X2 (crospovidone) significantly influence the dependent variables disintegration and friability. Results of characterization study revealed that solubility and dissolution of candesartan is increased due to conversion of crystalline drug to amorphous form by skimmed milk. The application of experimental design techniques to the optimization helps in reaching the optimum point in shortest time and minimum effort.

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