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Original Article

Solubility Enhancement of Candesartan Cilexetil by Mixed Solvency Approach

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ABSTRACT

Candesartan cilexetil is a pro-drug which has poor bioavailability because of poor solubility as it belongsto BCS class II. The aim of study is to enhance the solubility of candesartan cilexetil by mixed solvency approach. Solution was made by using different cosolvents to enhance solubility of candesartan cilexetil. Polyethylene glycol,ethanol, Tween 20 were used as solvents to increase solubility of candesartan cilexetil. A mixture of ethanol, tween 20, PEG 200 (1:1:1) and water was selected for solubility enhancement of candesartan cilexetil. FTIR study did not show any interaction between drug and excipients. Box-Behnken design was used for optimization offormulation.The mixture of drug, PEG 200, tween 20 and water was evaluated for drug content,% transmittance, pH, visual clarity. When the level of ethanol, tween 20 or PEG increased, the %transmittance increased. The stability study up to one month showed that no significan changes by evaluation parameter. Thus by applying mixed solvency approach to the candesartan cilexetil, solubility of candesartan cilexetil was increased thousand times as compared to drug alone.

Keywords: co-solvents, bioavailability, solubility enhancement, mixed solvency, Box-Behmken, %transmittance.

1. INTRODUCTION

Candesartan cilexetil is an antihypertensive drug which is used to control high blood pressure. Candesartan cilexetil is a BCS class II drug. It has poor solubility (0.012mg/ml) and poor bioavailability.[1, 2] Due to low solubility it requires high dose of concentration for therapeutic effectiveness of drug.

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Solubility is measured in terms of the maximum mass or volume of solute that will dissolved in a given mass or volume of solvent at a particular temperature and at equilibrium.[3] Solubility is an important parameter to achieve desire concentration of drug in systemic circulation for pharmacological response. Commonly employed techniques for solubilization include micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy etc.[4, 5] Mixed Solvency is one of the important technique (concept) recently developed to increase the solubility of poorly soluble drugs.[6].This approach shall prove a boon in pharmaceutical field to develop various formulations of poorly water-soluble drugs by combining various solvents in safe concentrations to produce a desirable aqueous solubility of poorly water soluble drug.In the present study, an attempt was made to increase the aqueous solubility of candesartan cilexetil using PEG 200, tween 20, ethanol as cosolvents.

2. MATERIALS AND METHODS

Candesartan cilexetil bulk drug was a gift sample from Centurion laboratories, Vadodara. All other chemicals and solvents used were of analytical grade.

2.1 Preparation of standard stock and calibration curve

Ten miligram candesartan cilexetil was dissolved in 10 ml methanol to obtain solution "A" (1000µg/ml). One mililitre of solution "A" was diluted upto 10 ml with methanol so as to obtain solution "B" (100µg/ml). 0.4, 0.6, 0.8, 1 and 1.2 ml of solution 'B' was pipetted and diluted with water to get 4, 6, 8,10 and 12 µg/ml concentration in 10 ml volumetric flask. The absorbance of each solution was measured at 254 nm against water as blank. The study was repeated at least three times and the value of mean and standard deviation was calculated.

2.2 Solubility study

Solubility study of candesartan cilexetil was measured by taking 10 mg drug in a test tube and solvent was added gradually in aliquots of 0.1 ml with continuous shaking until it dissolved completely. Solubility of drug was checked in ethanol, tween 20, PEG 200, propylene glycol, glycerol and hydrotopes such as sodium salicylate, sodium citrate, nicotinamide, sodium benzoate. Solubility was calculated and categorized as per descriptive terms given in Indian Pharmacopoeia 2010.[7]

2.3 Drug-Excipients compatibility study

Fourier transform infrared spectroscopy was carried out for liquid sample (drug, cosolvents and water), immediately after preparation and after storage for 7 days at accelerated conditions, to detect if any interactions were present between the drug and solvents. The sample was prepared by the potassium bromide disc method, 1 drop of liquid sample was added on 297mg KBr blank disc. The sample was transferred to sample compartment. Samples were scanned in the region of 4000- 400 cm^1 using a FTIR spectrometer. The spectrum obtained after storage was compared with initial spectrum of same mixture. Analysis of the formulation was also done for compatibility study of drug with excipients. Immediately after samplepreparation, drug content of sample was studied. After studied drug content of sample, the sample was stored in accelerated conditions at 60^0C for 7 daysand again drug content was performed for all samples.

2.4 Optimization

The optimized concentration of cosolvents in solubility enhancement of Candesartan cilexetil was determined by evaluating the critical parameters like % Transmittance, visual Clarity and absorbance. A conventional full factorial design with 3 factors and 3 levels (3^3) leads to 27 batches while Box-Behnken model required 17 batches for optimization. Thus, Box

Behnken Model was used for further statistical analysis. The dependent variables selected for statistical analysis were % Transmittance, Visual Clarity and Absorbance. Three levels (coded as -1, 0, +1) of these independent variables were decided to be studied (Table 1). Optimization offormulation was carried to get optimum concentration of Ethanol, Tween20 and PEG200 to obtain best solubility of poorly soluble drug. (Table 2)

Table 1: Optimization of formulation by Box-Behnken

Cosolvents (Factors)	Medium (%)		
	Low(-)	0	High(+)
Ethanol	25	27	29
PEG 200	25	27	29
Tween 20	25	27	29

Table 2: Box-Behnken Design with coded value of independent variable

Std	Run	Factor1 Ethanol	Factor 2 Tween 20	Factor3 PEG200
1	6	25	25	27
2	2	29	25	27
3	1	25	29	27
4	3	29	29	27
5	15	25	27	25
6	7	29	27	25
7	16	25	27	29
8	4	29	27	29
9	5	27	25	25
10	9	27	29	25
11	12	27	25	29
12	14	27	29	29
13	8	27	27	27
14	10	27	27	27
15	13	27	27	27
16	17	27	27	27
17	11	27	27	27

2.5 Evaluation parameters

Drug content

Drug content was measured by suitably diluting the solution with water and measuring by UV spectrophotometer at 254 nm, against water as blank.

% Transmittance

%Transmittance of solutions were checked by UV spectrophotometer at 650 nm. Transmittance showed the clarity of the solution. Solubility increased as well as % transmittance increased.

pH

pH of solutions of all batches was checked by digital pH meter.

Visual clarity

Visual clarity was checked by confirming the solution was clear or turbid. If precipitates were presented in the solution, the solution was concluded as turbid.

Stability Study

The stability study was carried out on the optimized formulation over the period of one month. Solutions of all batches kept in stability chamber maintained at 40 ± 2°C / 75 ± 5% RH for one month. At the end samples were analyzed for the % transmittance, pH, visual clarity, drug content. Another accelerated stability study was done at 60 ± 2°C / 75 ± 5% for 7 days, in order to get an idea of impact of temperature on the stability of candesartan solution.

3. RESULTS AND DISCUSSION

3.1 Calibration curve

λ_{max} determination

λ_{max} of candesartan cilexetill in water was found to be 255 nm by UV spectrophotometer.Calibration curve of candesartan cilexetill was prepared in water. Linearity was found in the concentration range of 4 to 20µg/ml with correlation coefficient (R^2) value was found to be 0.997 (Fig. 1).

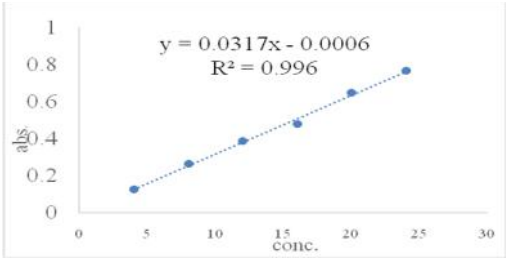

Fig 1: Calibration curve of candesartan cilexetil in water

3.2 Screening studies

Solubility study of candesartan cilexetil was determined in different solvents. On checking drug solubility in many cosolvents and hydrotopes, it was found that solubility of drug was increased by PEG200 and Tween20. It was also found that solubility of drug was not increased by propylene glycol, glycerol. Inspite of taking 50 ml solution of hydrotopes such as sodium citrate, sodium salicylate, nicotinamide, sodium benzoate for 10 mg of drug, solubility of drug was not increased. After that when took a combination of mixture of PEG 200 and Tween20 (1:1) for solubility, the solubility was more increased. After that when took a mixture of PEG 200, Tween 20 and Ethanol (1:1:1), the solubility was more increased.

Table 3: Evaluation of cosolvents and hydrotpes

Sr. No.	Cosolvents	Conc. (mg/ml).)
1.	PEG 200	10mg/ml
2.	Tween 20	8.33mg/ ml
3.	Ethanol	2.5mg/ml
4.	Propylene Glycol	Practically insoluble
5.	Glycerol	Practically insoluble
6.	PEG 200+Tween 20(1:1)	16.7mg/ml
7.	PEG 200 + Tween 20 + Ethanol (1:1:1)	25.0mg/ml
8.	Sodium salicylate	Not soluble in more than 50ml.
9.	Sodium citratre	Not soluble in more than 50ml.
10.	Sodium benzoate	Not soluble in more than 50ml.
11.	Nicotinamide	Not soluble in more than 50ml.

3.3 Drug Excipients compatibility study by FTIR

FTIR of solution of drug and solvent mixture (Ethanol+ Tween 20+ PEG 200(1:1:1)) and water was taken immediately as initial and after 7 days storage at 40^{o}C/ 75% RH. When compared, the peak of the initial spectrum (Fig. 2) to the peak of spectrum after 7 days storage (Fig. 3), it was observed that there was no incompatibility among the drug & excipients, even on storage. Chemical analysis of the formulationwas also done to check the compatibility of drug with excipients of final composition. The drug content of sample (Initial and after storage for 7 days at accelerated condition) was determined spectrophotometrically, at 255nm after suitable dilutions. It was observed that there was no significant difference in solutioneven after storage. So, it was decided that candesartan cilexetil (drug) was compatible with excipients.

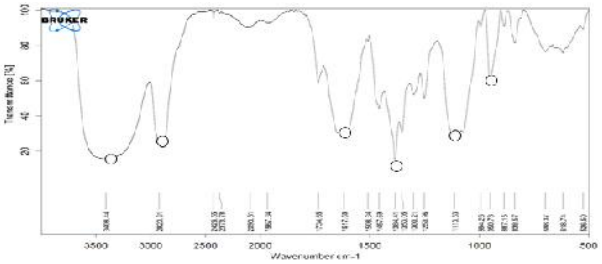

Fig 2: FTIR of Sol.ofDrug+mix.(Ethanol+Tween 20+PEG 200)+water (Initial)

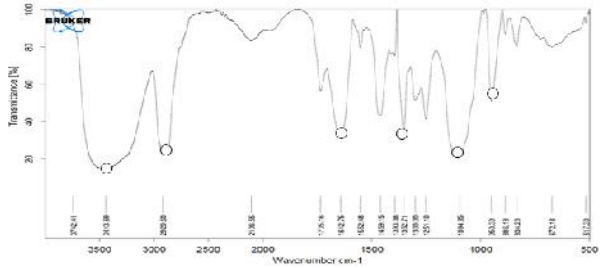

Fig 3: FTIR of Sol.of Drug+mix.(Ethanol+Tween 20+PEG 200)+water after 7 days

3.4 Optimization

Optimization was done by using Box-Behnken design. The co-solvents such as Ethanol, Tween 20, PEG 200 were used as independent variables. Responses considered were visual clarity, %transmittance and absorbance. Among all batches batch no.12 was showing 100% transmittance. It was observed that as the concentration of polysorbate 20, PEG 200 and ethanol increased, there was increased in % transmittance. In other batches such as batch no.13 to 17, concentration not showing good result as more the concentration of tween 20, PEG 200 solubility as per the transmittance. Statistical analysis for %

transmittance was done using design of experiment DX9 software. The software suggested Quadratic model and obtained design table is shown in table 4.

Table 4: Visual clarity, %Transmittance, Absorbance for optimization

Std	Ethanol	Tween 20	PEG 200	PPT	%Transmittance (at 650 nm)	Absorbance (at 420nm)
1.	25	25	27	Y	-	-
2.	29	25	27	Y	-	-
3.	25	29	27	Y	-	-
4.	29	29	27	-	99.1	0.245
5.	25	27	25	Y	-	-
6.	29	27	25	-	99.8	0.185
7.	25	27	29	-	99.2	0.202
8.	29	27	29	-	99.5	0.198
9.	27	25	25	Y	-	-
10.	27	29	25	-	99.7	0.178
11.	27	25	29	-	99.9	0.274
12.	27	29	29	-	100.9	0.207
13.	27	27	27	-	95.4	0.246
14.	27	27	27	-	96.4	0.182
15.	27	27	27	-	96.7	0.224
16.	27	27	27	-	94.2	0.208
17.	27	27	27	-	95.7	0.215

3.5 ANOVA for transmittance

All the factors showed pp value < 0.05, i.e. significant effect on % transmittance. The equations represent the quantitative effect of variable (A, B and C) and their interaction on transmittance (Y1).

Full equation

$Y1= +96.2 +24.90A+ 24.98 B+ 25.00 C + 24.77AB– 24.68 BC– 24.88 AC– 35.92 A^2 – 35.42 B^2+ 14.43 C^2$….

A coefficient with positive sign represents the synergistic effect of the transmittance, while negative sign indicate antagonist effect. Transmittance increased with the concentration of Tween 20, PEG 200 and ethanol increased. Significant interaction was found between the cosolvents, as evident from the P-value < 0.05. %Transmittance increased with increase in combination level of Ethanol and tween 20. %Transmittance decreased with increase in combination level of PEG 200 and tween 20. %Transmittance decreased with increase in combination level of Ethanol and PEG 200. From the observation, it can be concluded that combination of PEG 200 and tween 20 showing negative effect on % transmittance. This observation is plotted in counter plot and response surface plot. (Fig.4, 5, 6)

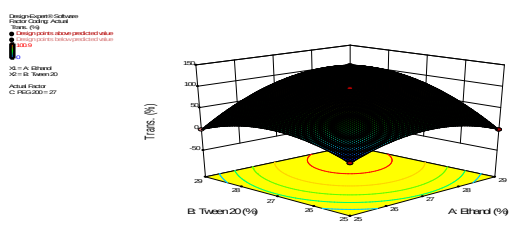

Fig 4: Response surface plot of transmittance (Y1)(AB)

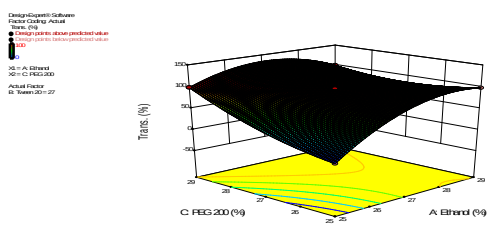

Fig 5: Response surface plot of transmittance (Y1)(AC)

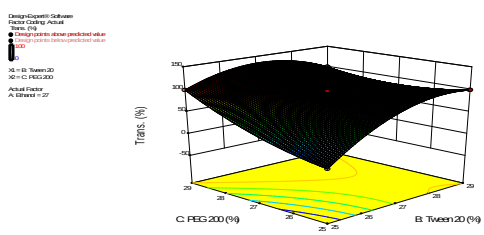

Fig 6: Response surface plot of transmittance (Y1) (BC)

Table 5: pH of all no of batches

Sr.no.	Batches	PH
1.	4	4.57
2.	6	4.56
3.	7	4.56
4.	8	4.58
5.	10	4.57
6.	11	4.51
7.	12	4.58
8.	13	4.59
9.	14	4.62
10.	15	4.63
11.	16	4.64
12.	17	4.62

Table 6: Stability study of solutions

Batch no.	%Initial Drug content	%Drug content after 7 days at 60^0C	%Drug content after 1month at 40^0C
4	102.3	101.4	100.82
6	99.24	98.6	98.29
7	99.55	99.24	99.24
8	100.1	99.5	100.1
10	98.29	98.29	98.29
11	98.11	98.29	98.29
12	102.71	101.7	102.31
13	99.24	98.92	98.92
14	99.80	99.55	99.55
15	99.87	99.55	99.24
16	99.55	98.61	98.92
17	99.87	99.55	98.29

3.6 Evaluation of number of batches

Solutions of batches no. 1 to 17 were evaluated for drug content, pH, %transmittance, visual clarity. Solutions of batches 1, 2, 3 and 5 were showing precipitation as other batches were clear. Drug content was measured according to the procedure mentioned as earlier. It was evaluated and observed that all the following batches have approximately 100% drug content. So, it was concluded that drug is showing high solubility in above solvents. % Transmittance showed the clarity of the solution. Clarity of the solution depends on solubility of drug. Solutions of batches no. 4 to 17 showed good clarity. Solutions of batch no.1 to 3 and 5 were failed in clarity test. It was observed precipitation within some period of time. % transmittance of all formulated batch is recorded in table no.4The prepared solutions were subjected to surface pH measurement by digital pH meter. pH values were observed in range of 4.51 to 4.62.

3.7 Stability study

Stability studies indicated that, no significant changes (Table 6) were observed with respect to % drug content on storage at 60± 2^0C for 7 days and ICH accelerated condition (40± 2^0C/75 %±5% RH) for 1 month. It indicates that, all batcheswere stable in following condition, Clarity of the solutions was checked by % transmittance at 650 nm using UV spectrophotometer. Comparing the transmittance of the solutions between before storage and after storage, no significant changes were observed in % transmittance of the solutions. So, it was concluded that solutions were stable.

4. CONCLUSION

Soiubility of candesartan cilexetil was enhanced successfully using cosolvents with the optimized formulation parameter of liquid solution with acceptable % transmittance at 650 nm, absorbance at 420nm and pH were obtained. Enhancement of solubility was achieved by the increase in %transmittance. When level of ethanol, tween 20, PEG 200 increased, transmittance increased. % Transmittance was effected on solubility. When the solubility of a mixture solution was high, it showed more clarity. Solubility of candesartan cilexetil in water is 0.012 mg/ml. Solubility of drug in mixture of cosolvents (PEG200, Tween 20, ethanol(1:1:1)) was found to be 25mg/ml which is thousand times as compared to the reported aqueous solubility of the drug alone.

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