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Research Article

PREPARATION AND *IN VIVO* EVALUATION OF CANDESARTAN CILEXETIL SOLID DISPERSIONS

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ABSTRACT

Objective: The present study aims at development of solid dispersions (SD) of candesartan cilexetil for enhanced solubility and bioavailability.

Methods: About 18 SD formulations of candesartan cilexetil were prepared by solvent evaporation technique and evaluated. The *in vitro* release studies were conducted and the best formulation chosen was further characterized for Fourier transform infrared spectroscopy, Scanning electron microscope, X-ray, and stability. The *in vivo* evaluation study conducted in rats.

Results: The formulation SD16 containing drug and Soluplus in 1:3 ratio along with 2% selective laser sintering was chosen optimal based on drug content (99.08%), and drug release (99.7%). *In vivo* studies conducted on SD16 showed that mean time to peak concentration (T_{max}) was 2.0±0.05 and 4±0.2 h for the optimized and pure drug, respectively, while mean maximum drug concentration (C_{max}) was 570.63±2.65 ng/mL and was significant as compared to the candesartan pure drug 175.146±0.07 ng/mL. Area under curve $AUC_{0-\infty}$ infinity for candesartan SD16 was higher (4860.61±1.05 ng.h/ml) than pure drug suspension 1480±1.72 ng.h/ml.

Conclusion: Hence, the developed SD formulations enhanced the bioavailability of drug by 3 folds.

Keywords: Candesartan cilexetil, Hypertension, Solid dispersions, Solubility, Soluplus, Poloxamer, *In vivo* bioavailability studies.

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INTRODUCTION

Candesartan that is used in treating hypertension and heart misfunction, suffers from meager aqueous solubility, efflux by intestinal p-glycoprotein, and vulnerable towards enzymatic degradation in stomach [1-3]. These drawbacks can be overcome either by chemical or mechanical modification of environment surrounding the drug substance, or physically altering the characteristics of aggregated drug particles [4,5].

Several methods can be employed to obtain a solid dispersion (SD) to enhance drug solubility and bioavailability [6]. SD comprises of a hydrophilic matrix, and a hydrophobic drug. Hydrophilic carriers include Povidone (Polyvinyl pyrrolidine [PVP]), Polyethylene glycols (6000, 8000) [7,8]. The SD is dispersion of drug in an amorphous matrix in which the drug exists in molecularly dispersed phase [9].

This study aims to develop and evaluate various SD formulation of candesartan cilexetil (CAC) for enhancing bioavailability.

METHODS

Material

The CAC was gift sample from Aurobindo Pharm Ltd, Hyderabad, India. Poloxamer 407 and PEG 8000 purchased from BASF, India. Kolliwax GMS purchased from Signet Chem Corp. Pvt. Ltd, Mumbai. Soluplus was gift sample from BASF, Germany. PVP K-30 was gifted from Dow Chem, USA.

Formulation and evaluation of CAC SD [10]

Twenty formulations of SDs (SD1-SD20) were prepared using various polymers and selective laser sintering (SLS) as per the procedure referred in [10]. All the formulations are evaluated for % practical yield, drug content, and drug release as per referred procedures (Table 1) [11-13].

Characterization of SD formulations

All the 20 formulations were characterized for Fourier transform infrared spectroscopy, Powder X-ray diffraction (XRD) and scanning electron microscope (SEM) as per the referred procedures [10,14-16].

Stability studies

The optimized formulation subjected to stability study at 75±5% RH 40°C±2°C for 3 months and evaluated periodically [17].

Pharmacokinetic studies of CAC SD

Animal preparation

Wistar rats (150–180 g) maintained under restricted environmental condition (25°C, 45% RH and 12 h alternating light/dark cycles) with complete clean air exchange, continuous electricity and water supply in the animal room. Rats provided with regular diet and water *ad libitum*. The study was approved by the institutional animal ethics committee (IAEC NO: 1292/ac/09/CPCSEA/47/A).

Study design

All the animals were categorized into two groups. The rats fasted for 24 h before the experiments. After 4 h of dosing, food was reoffered.

Group I: Administrated with pure CAC suspension in 0.5% methocel.
Group II: Administrated with CAC optimized SD diluted in 0.5% methocel orally at a dosage of 0.25 mg.

Then, 200 µL blood samples taken out from the femoral artery at specific time intervals till 24 h post-dose and mixed with heparin to retard blood clotting. The plasma isolated by centrifugating the sample at 5000 rpm for 5–10 min followed by storage at −20°C [18].

Table 1: Composition of CAC SD

Formulation no and Ingredients	Candesartan (gm)	PVP K30 (gm)	Poloxamer (gm)	Kolliwax GMS (gm)	Soluplus (gm)	PEG 8000	SLS (gm)	Methanol (mL)
SD 1	0.16	0.16	–	–	–	–	0.0	Quantum satis
SD 2	0.16	0.16	–	–	–	–	2.0	Quantum satis
SD 3	0.16	0.48	–	–	–	–	0.0	Quantum satis
SD 4	0.16	0.48	–	–	–	–	2.0	Quantum satis
SD 5	0.16	–	0.16	–	–	–	0.0	Quantum satis
SD 6	0.16	–	0.16	–	–	–	2.0	Quantum satis
SD 7	0.16	–	0.48	–	–	–	0.0	Quantum satis
SD 8	0.16	–	0.48	–	–	–	2.0	Quantum satis
SD 9	0.16	–	–	0.16	–	–	0.0	Quantum satis
SD 10	0.16	–	–	0.16	–	–	2.0	Quantum satis
SD 11	0.16	–	–	0.48	–	–	0.0	Quantum satis
SD 12	0.16	–	–	0.48	–	–	2.0	Quantum satis
SD 13	0.16	–	–	–	0.16	–	0.0	Quantum satis
SD 14	0.16	–	–	–	0.16	–	2.0	Quantum satis
SD 15	0.16	–	–	–	0.48	–	0.0	Quantum satis
SD 16	0.16	–	–	–	0.48	–	2.0	Quantum satis
SD 17	0.16	–	–	–	–	0.16	0.0	Quantum satis
SD 18	0.16	–	–	–	–	0.16	2.0	Quantum satis
SD 19	0.16	–	–	–	–	0.48	0.0	Quantum satis
SD 20	0.16	–	–	–	–	0.48	2.0	Qs

CAC: Candesartan cilexetil, PVP: Polyvinyl pyrrolidine, SD: Solid dispersions.

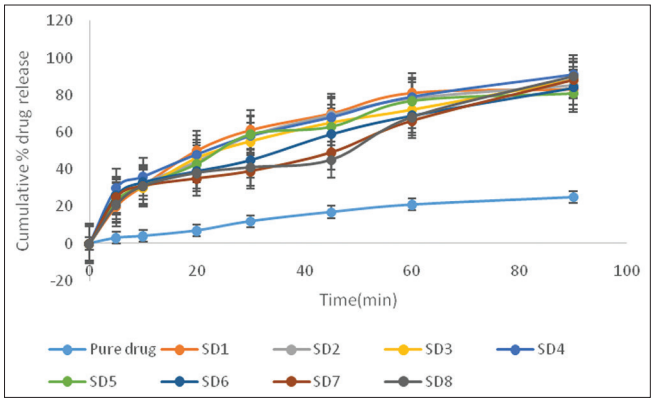

Fig. 1: Drug dissolution of pure drug and formulations solid dispersions (SD)1-SD8

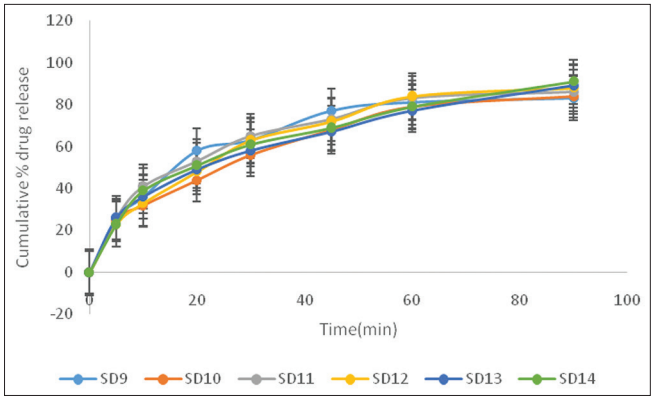

Fig. 2: Drug dissolution of formulations solid dispersions (SD)9-SD14

Determination of CAC by HPLC method

The chromatographic separation of CAC was achieved on Waters Reliant C18 column (250 mm × 4.6 mm, 5 µm protected by a precolumn guard cartridge using ACN-5 mM sodium acetate (80:20, v/v) (pH adjusted to 3.5 with CH_3COOH as mobile phase at a flow rate of 0.8 mL/min). The analyte was monitored at 234 nm. The temperature of the analytical column was set at 30°C [19].

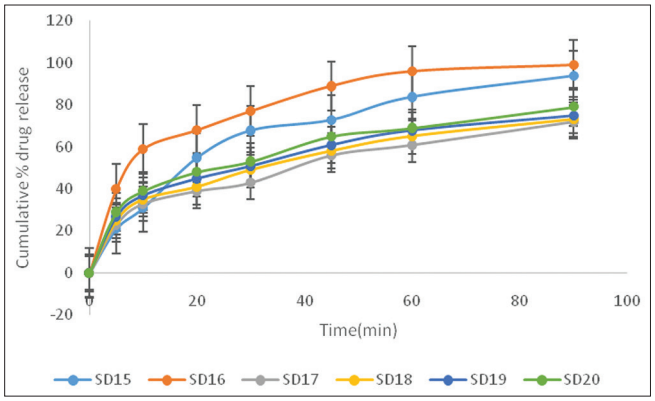

Fig. 3: Drug dissolution of formulations solid dispersions (SD)15-SD20

Pharmacokinetic analysis

The pharmacokinetic parameters evaluated include C_{max}, T_{max}, t ½, Area under curve $(AUC)_{0-\infty}$, AUC_{0-t}.

RESULTS AND DISCUSSION

Evaluation of SD formulations

The % practical yield of all formulations ranged between 83.88% and 99.28% with maximum yield observed for SD16. The drug content ranged between 86.33% and 99.08% with maximum value observed for SD16. Maximum *in vitro* drug release profile was displayed by SD16 (99.7±4.2%) (Figs. 1-3) [10].

Characterization of optimized SD formulation

The IR spectra of SD16 displayed all characteristic peaks of drug indicating the compatibility between drug and excipients (Fig. 4 and 5).

XRD patterns

The XRD of SD16 was characterized by nonexistence of diffraction peaks, which is trait of an amorphous composition (Fig. 6 and 7).

SEM studies

The SEM studies of SD16 show that the drug crystals are completely incorporated into polymer matrix which might be due to complete dispersion of CAC in molten polymer (Fig. 8).

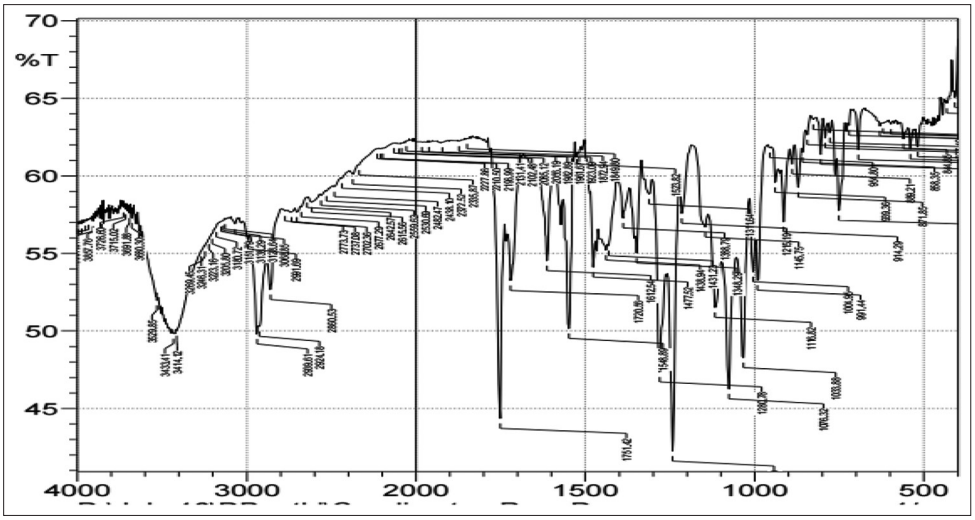

Fig. 4: Fourier transform infrared Spectrum of candesartan cilexetil

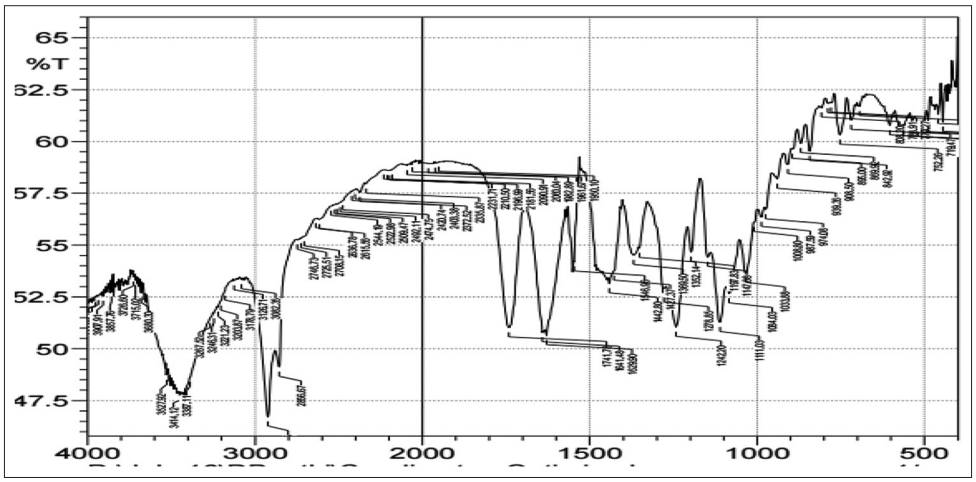

Fig. 5: Fourier transform infrared spectrum solid dispersions 16

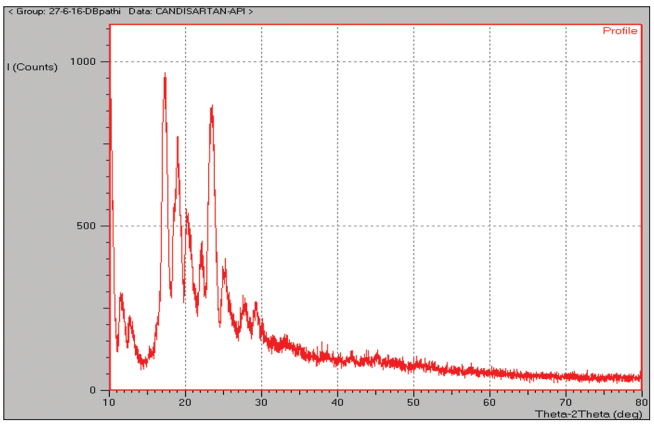

Fig. 6: X-ray diffraction of candesartan cilexetil

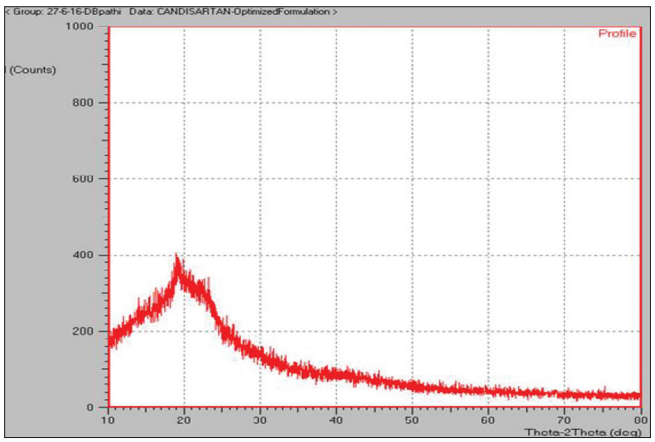

Fig. 7: X-ray diffraction of candesartan cilexetil optimized formulation solid dispersions 16

Stability study

The formulation SD16 was found is stable for 3 months and holds their original properties with minor variations (Table 2).

Pharmacokinetic parameters comparison for candesartan pure drug and optimized SDs

Fig. 9 and 10 indicate plasma concentration-time curve recorded post single oral dose of candesartan optimized SD formulation in comparison to candesartan pure drug suspension. At any time, the drug plasma concentrations in animals administrated with optimized SD were higher than pure drug (Table 3 and Fig. 11).

C_{max} of the candesartan optimized SD 570.63±2.65 ng/ml was significant ($p<0.05$) when compared to CAC drug suspension (175.146±0.07 ng/ml).

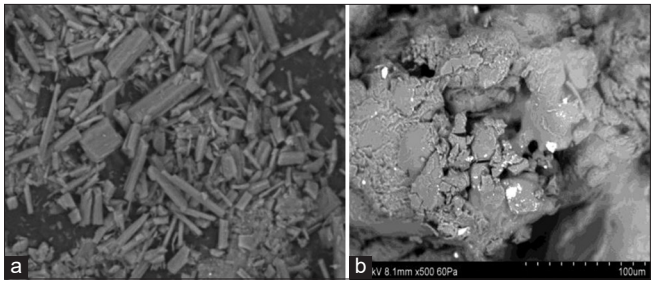

Fig. 8: Scanning electron microscope photographs of (a) candesartan and (b) solid dispersions 16

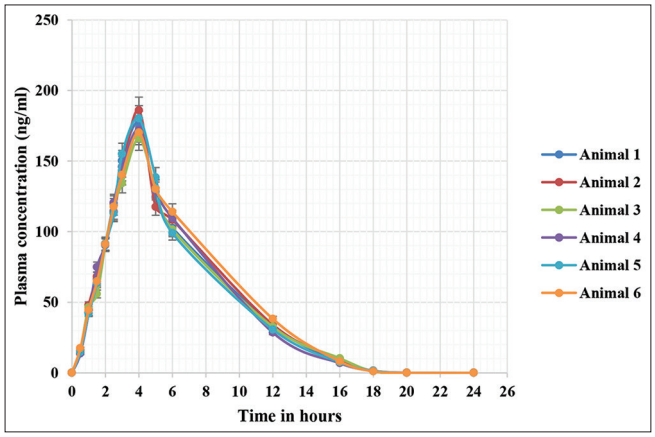

Fig. 9: Plasma concentration-time profile of CAC in rat plasma

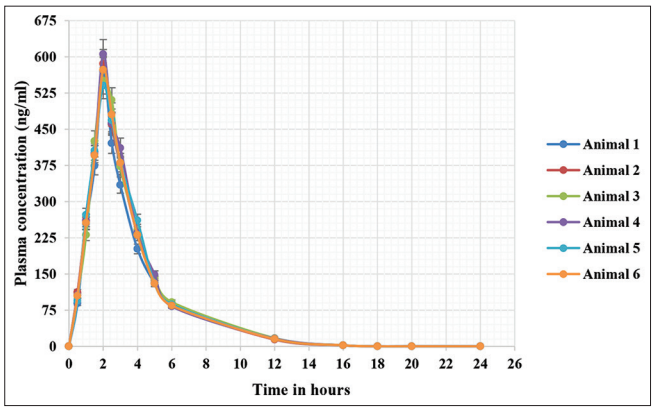

Fig. 10: Plasma concentration-time profile of candesartan cilexetil optimized solid dispersions in rat plasma

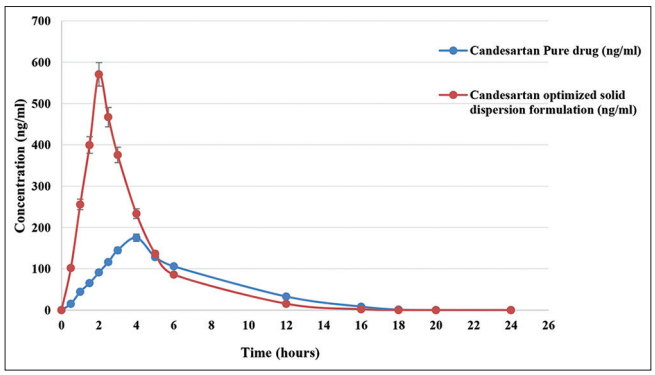

Fig. 11: Plasma concentration profiles of candesartan cilexetil (CAC) optimized solid dispersions and CAC

Table 2: Stability studies of SD16 at 40±20°C/75±5% RH

Retest time (days)	% Drug content	*In-vitro* drug release (%)
0	99.08	99.70
30	98.39	98.55
60	97.65	97.45
90	96.05	96.15

SD: Solid dispersions.

Table 3: Pharmacokinetic studies of CAC optimized SD and pure drug

Parameters	CAC	CAC optimized SD
C_{max} (ng/ml)	175.146±0.07	570.63±2.65
AUC_{0-t} (ng.h/ml)	1420±1.24	4516.64±1.18
AUC_{0-inf} (ng.h/ml)	1480±1.72	4860.61±1.05
T_{max} (h)	4±0.2	2.0±0.05
$t_{1/2}$ (h)	10±0.42	8.02±0.04

CAC: Candesartan cilexetil, SD: Solid dispersions.

T_{max} of optimized SD formulation and the pure drug was 2.0±0.05 and 4±0.2 h, respectively. AUC0-∞ infinity for candesartan optimized SD formulation was higher (4860.61±1.05 ng.h/ml) than the CAC suspension 1480±1.72 ng.h/ml. Statistically, AUC0-t of the optimized SD formulation was significantly higher ($p<0.05$) as compared to the pure drug suspension formulation. A higher concentration of drug in blood is indicative of improved absorption of candesartan from SD formulation when compared to the drug suspension formulation.

CONCLUSION

Among all the 20 SD formulations prepared with varying concentration of polymers the formulation SD16 comprising Soluplus and drug in 3:1 ratio displayed maximum dissolution of 99% which can be attributed to the raise in drug wettability, switch to amorphous form and solubilization of drug due to hydrophilic carrier. *In vivo* studies revealed that C_{max} of the candesartan optimized SD 570.63±2.65 ng/ml was significant ($p<0.05$) as compared to the pure drug suspension formulation 175.146±0.07 ng/ml. T_{max} of both optimized SD f and pure drug were 2.0±0.05 and 4±0.2 h, respectively. $AUC_{0-\infty}$ infinity for candesartan optimized SD formulation was higher (4860.61±1.05 ng.h/ml) than pure CAC (1480±1.72 ng.h/ml). The results show that SDs are most favorable formulations for CAC delivery for efficient management of hypertension.

CONFLICTS OF INTERESTS

No conflicts of interest.

AUTHORS CONTRIBUTION

Mr. Ashok carried out the experiment, wrote the manuscript with support from Dr Gande Suresh who also helped supervise the project.

AUTHORS FUNDING

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REFERENCES

1. Aboul FK, Allam AA, El-Badry M, El-Sayed AM. Development and *in vitro*/*in vivo* performance of self-nanoemulsifying drug delivery systems loaded with candesartan cilexetil. Eur J Pharm Sci 2017;15:503-13.
2. Shafiq S, Shakeel F, Talegaonkar S, Ahmad F, Khar R, Ali M. Development and bioavailability assessment of ramipril nanoemulsion formulation. Eu J Pharm Biopharm 2007;66:227-43.
3. Pathak K, Raghuvanshi S. Oral bioavailability: Issues and solutions via nanoformulations. Clin Pharmacokinet 2015;54:325-57.
4. Kasturi M, Agarwal S, Yadav JK. Self-nano-emulsifying drug delivery

system of ramipril: Formulation and *in-vitro* evaluation. Int J Pharm Pharm Sci 2016;8:975-1491.
5. Ali HH, Hussein AA. Oral solid self-nanoemulsifying drug delivery systems of candesartan citexetil: Formulation, characterization and *in vitro* drug release studies. Apps Open 2017;3:1-12.
6. Patel TB, Patel LD, Patel TB, Makwana SH, Patel TR. Formulation and characterization of solid dispersions containing glibenclamide. Int J Pharm Pharm Sci 2010;2:975-1491.
7. Bhikshapathi DV. Development and *in vitro* evaluation of solid dispersions of candesartan cilexetil. Asian J Pharm Clin Res 2019;12:233-41.
8. Yamashita K, Nakate T, Okimoto K. Establishment of new preparation method for solid dispersion formulation of tacrolimus. Int J Pharm 2003;267:79-91.
9. Dasi S, Roy S. Solid dispersions: An approach to enhance the bioavailability of poorly water-soluble drugs. Int J Pharmacol Pharm Technol 2008;3:227-4.
10. Kumar UA, Suresh. Development and *in vitro* evaluation of solid dispersions of candesartan cilexetil. Asian J Pharm Clin Res 2019;12:233-4.
11. Lakshmi K, Reddy MP, Kaza R. Dissolution enhancement of telmisartan by surface solid dispersion technology. Int J Innov Pharm Sci Res 2012;3:247-51.
12. Shingala K, Chetan S, Deepak D. Formulation development and evaluation of immediate release tablet of poorly soluble candesartan cilexetil. J Pharm Sci Biosci Res 2013;3:77-90.
13. Valizadeh H, Nokhodchi A, Qarakhani N. Physicochemical characterization of solid dispersions of indomethacin with PEG 6000, Myrj 52, lactose, sorbitol, dextrin, and Eudragit E100. Drug Dev Ind Pharm 2004;30:303-17.
14. Yang M, Wang P, Huang CY. Solid dispersion of acetaminophen and poly(ethylene oxide) prepared by hot-melt mixing. Int J Pharm 2010;395:53-61.
15. Shamma RN, Basha M. Soluplus®: A novel polymeric solubilizer for optimization of carvedilol solid dispersions: Formulation design and effect of method of preparation. Powder Tech 2013;237:406-14.
16. Breitenbach J. Melt extrusion: From process to drug delivery technology. Eur J Pharm Biopharm 2002;54:107-17.
17. Dhirendra K, Lewis S, Udupa N. Solid dispersions: A review. Pak J Pharm Sci 2009;22:234-46.
18. Patel M, Kothari C. Quantitative bio-analysis of pitavastatin and candesartan in rat plasma by HPLC-UV: Assessment of pharmacokinetic drug-drug interaction. J Chrom B 2019;1138:121962.
19. Narendar D, Kishan V. Candesartan cilexetil loaded solid lipid nanoparticles for oral delivery: Characterization, pharmacokinetic and pharmacodynamic evaluation. Drug Deliv 2016;23:395-404.