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Original Article

INVESTIGATION OF SOLID DISPERSION APPROACH FOR THE IMPROVEMENT OF PHARMACEUTICAL CHARACTERISTICS OF TELMISARTAN USING A CENTRAL COMPOSITE DESIGN

RITU[1], RAVINDER VERMA[2], VIKAS BUDHWAR[1], DEEPAK KAUSHIK[1*]

[1]Department of Pharmaceutical Sciences, Maharishi Dayanand University, Rohtak-124001, India. [2]Department of Pharmaceutical Sciences, Chaudhary Bansi Lal University, Bhiwani-127021, India
[*]Corresponding author: Deepak Kaushik; [*]Email: deepkaushik1977@gmail.com

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ABSTRACT

Objective: The goal of this study was to use a solid dispersion approach to improve the aqueous solubility and dissolution rate of Telmisartan.

Methods: Design of experiment trials was conducted following a central composite design with different combinations of polymers and stirrer rpm and the selected responses (drug release, entrapment efficiency) were determined. The selected optimized formulation was characterized by Fourier-transform infrared spectroscopy, differential scanning calorimetry, scanning electron microscopy, and X-ray diffraction, which reflected the changes that occurred in API and excipients after conversion in to the formulation.

Results: In the design of experiments, central composite design was implemented and it was observed that polymers concentration (polyvinyl pyrrolidine K25, polyethylene glycol 4000) and stirrer rpm were having a significant impact on the responses (drug release, entrapment efficiency), and variables were having p-value<0.05 which reflected the significant impact. The results of stability study showed a significant no decrease in drug assay values, which reflected the stability behavior of the formulation. The results of comparative dissolution studies revealed that the optimized formulation have improved the drug solubility and dissolution rate.

Conclusion: It can be concluded that optimized telmisartan-loaded solid dispersion improved the solubility and dissolution rate of Telmisartan. The optimized formulation was having release>85% release within 30 min. Further, the stability of the formulation was also assessed under the accelerated condition as per ICH which reflected their stability. So, this approach can be employed for improving dissolution rate of other BCS II class drugs.

Keywords: Telmisartan, Polyvinyl pyrrolidine K25, Polyethylene glycol 4000, Solid dispersion, Solvent evaporation, Central composite design

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INTRODUCTION

Modern drug discovery techniques, with advances in combinatorial chemistry and high throughput screening, continue to fill drug development pipelines with a high number of poorly soluble new chemical entities (NCEs). It is estimated that over the years, about 40%–70% of NCEs are poorly water soluble and a large number of scientists are engaged in the invention of NCEs and the success rate is poor. A drug with poor aqueous solubility will typically exhibit a dissolution rate of limited absorption, and a drug with poor membrane permeability will typically exhibit a permeation rate of limited absorption. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include: enhancing the solubility and dissolution rate of poorly water-soluble drugs and enhancing the permeability of poorly permeable drugs [1].

Scientists create a variety of active pharmaceutical ingredients (API), but the majority of compounds now being developed for oral dosage forms have solubility and dissolving issues, which are major challenges in the development of oral dosage forms and the discovery of new drugs. Compounds with low water solubility-typically less than 0.1 mg/ml-present unusual difficulties for drug research. Absorption of the drug is constrained by solubilization and dissolution [2, 3]. The use of amorphous forms, co-solvation, and super disintegrants, as well as the preparation of drugs, the decrease of crystal size, the transformation of drugs into prodrugs, the impregnation of liquid API and its API solutions in porous powders, the use of surface-active self-emulsifying systems, micronization, the formation of inclusion complexes with cyclodextrin (CD), the preparation of amorphous drugs. Although it is normal practice to use salt production and particle size reduction to speed up oral absorption, both methods do have significant practical drawbacks [4-7]. With neutral chemicals and weak electrolytes, salt production is not possible. On the other hand, due to their poor wetting ability, very thin powders of hydrophobic medicines are challenging to dissolve in water. Liquid drug loading into porous powder, often known as "powder solutions," encounters problems with flow properties and compressibility [8, 9]. In this research article, solid dispersion (SD) of telmisartan (TLM) has been prepared as a combination of hydrophilic polymers and also studies the impact of various variables on drug release and entrapment efficiency [9].

SD is a technology for the formulation of a drug having low solubility. Particularly, the formation of SD technique has been effectively used to produce formulations, including pharmaceuticals with high drug content and/or high crystallization potential. SD is described as the drug being dispersed in an amorphous polymer matrix, preferably with the drug in a molecular form [10, 11]. TLM is an angiotensin receptor blocker of biopharmaceutical classification system class II drugs and is used to treat blood pressure and reduce the risk of cardiovascular diseases. TLM is categorized as a biopharmaceutical classification system (BCS) class II drug because of its poor water solubility and high permeability. TLM has a weak water solubility that causes a delay in the drug's oral bioavailability. TLM oral bioavailability would therefore increase if its solubility could be increased [12, 13]. TLM amphoteric nature and ease of ionizability suggest that its solubility is pH-dependent. TLM has been found to have a solubility of less than 1 g/ml in the pH range of 3 to 9. TLM pKa value was reported to be 4.45 [14, 15].

As TLM is a BCS class II drug, hence it is having low solubility; with the solid dispersion technique, wettability of the drug can be increased by using various hydrophilic polymers like PVP, PEG etc. Thus by using the solid dispersion technique solubility of low-soluble drugs can be enhanced significantly. So, this research aimed to improve the solubility and dissolution rate of Telmisartan using a solid dispersion technique with the help of an optimization approach.

MATERIALS AND METHODS

TLM was obtained from Virchow drugs limited; PVP K25 and PEG 4000 were bought from Loba Chemie Pvt. Ltd. India. All additional

compounds used in the study were chosen to be of the analytical grade and were used exactly as the manufacturer had intended. Telmitan® 20 mg, Batch no. ARBS0141 Nest Health Care Pvt Limited was procured from a community pharmacy. The structure of telmisartan is mentioned in fig. 1.

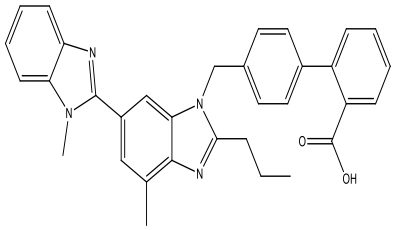

Fig. 1: **Structure of telmisartan**

Preparation and optimization of solid dispersion (SD)

SDs were prepared by solvent evaporation technique, drug equivalent to 20 mg was taken with different quantities of polymers in an adequate amount of methanol in a beaker and stirred with a magnetic stirrer for 30 min on a different rotation per minute (rpm) as given in the design of experiments (DoE) plan on digital magnetic stirrer with a hot plate (temp. not more than 40 °C). After that solvent was evaporated at 45 °C till complete evaporation. The solid dispersion prepared was pulverized in mortar and sieved. Thus SD was being prepared and equivalent to 20 mg of telmisartan encapsulated in a hard gelatine capsule shell [16]. Variables effect i.e., Polyvinylpyrrolidone K25 (PVP K25), Polyethylene glycol 4000 (PEG 4000), rotation per minute (rpm) of magnetic stirrer-on entrapment efficiency and drug release % in Phosphate Buffer (PB) pH 7.5 were being studied using a central composite design by Design Expert® software, version 11.0.4.0. The criteria and levels of independent variables that were picked are listed in table 1.

Table 1: Levels of independent variables

Factor	Variables	Low level (-1)	Medium (0)	High level(+1)
A	PEG 4000 (mg)	20	110	200
B	PVP K 25 (mg)	20	100	180
C	Stirring time (RPM)	100	200	300

Twenty trial runs were created using the design expert® software, version 11.0.4.0, as, in which the concentration of the polymers and rpm were changed while the amount of drug used remained the same. Experiments were performed for 20 twenty trials and the responses were examined using ANOVA $p<0.05$, by the best-fitting model. Drug dose was kept constant i.e. 20 mg [17-19].

***In vitro* dissolution studies of TLM SD**

USP apparatus II (paddle) was used for the *in vitro* dissolution test. The dissolution medium was phosphate buffer (pH 7.5) at 37 °C±0.5 °C. 75 rpm was used in 900 milliliters of the dissolving media. After starting the rotation of the paddles, a capsule containing TLM SD formulation equivalent to 20 mg of TLM was added to the dissolution medium. Five-milliliter samples were taken out 10, 20, and 30 min later. Following sample collection, an equivalent volume of the new medium was added to the media to maintain a constant volume of dissolution. By using a UV Spectrophotometer at 296 nm, the samples were examined [20-22].

Entrapment efficiency (%)

SD equivalent to 20 mg was dissolved in 10 ml methanol and further volume was made up of phosphate buffer 7.5 up to 100 ml and a further 1 ml diluted up to 10 ml (20 ppm solution). Absorbance at 296 nm of all the trials was taken and the amount of TLM was determined, which was further compared with theoretical absorbance from the linearity plot of standard [23-25].

$$\text{Entrapment Efficiency} = \frac{\text{Theoretical concentration} - \text{Observed concentration}}{\text{Theoretical concentration}} \times 100$$

Characterization

Differential scanning calorimeter (DSC)

DSC was carried out on DSC Q10 V9.9 Build 303. Purified indium (99.99%) was used to calibrate the instrument. Models (5 mg) were sealed in an aluminum pan with a flat bottom (Shimadzu DSC-60, Japan). This pan was put into the DSC device and scanned at a rate of 10 °C/min between 30° and 300 °C. With a flow rate of 10 ml/min, nitrogen was utilised as a carrier gas to completely reverse the oxidative and pyrolytic effects [26-28].

Fourier-transform infrared spectroscopy (FT-IR) studies

FT-IR can be used to characterise potential interactions between API and carrier in the solid state. The FT-IR was obtained using an FT-IR Spectrophotometer (The FT-IR of the inclusion complexes was performed on (FT-IR Bruker Shimadzu, Japan) and a dried sample of pure TLM, PEG 4000, PVP K 25, physical mixing, and SD-formulation. The observed peaks are identified for the functional group [29].

X-ray diffraction (XRD) analysis

A technique for examining the atomic or molecular structure of materials is XRD. It is non-destructive and works well with totally or partly crystalline materials. Holding the taster firmly in place while pressing the stage-up button with the other hand locks the sample into place on the instrument. According to the protocol, the slits in the "anti-scattering" and "detector" locations are checked. The doors then slowly and softly connect as they move together. After locking the doors, the computer expands "XRD commander" and, if necessary, increases power. An automatic save is done after the scan. After the task is complete, the taster is taken out and the enclosure's doors are shut. The XRD spectra of the pure TLM, PEG 4000, PVP K 25, PM and optimised formulation were recorded at room temperature using XRD (X'Pert XRD Powder type PW 30/40 panalytical, the Netherlands) with a voltage of 40 kV, 40 mA current and degree of crystallinity determined [30, 31].

Scanning electron microscopy (SEM) analysis

A targeted electron beam is used to scan a sample's surface in a scanning electron microscope (SEM), which creates pictures of the sample. The sample's surface topography and chemical composition are revealed by the signals that are created as a result of the electron interactions with the sample's atoms. Because of its excellent resolution and high magnification, a physicochemical characterisation is a helpful approach that is frequently used to evaluate the solid-state characteristics of medications, polymers, and formulations. Scanning electron micrographs were then taken using a JEOL JSM 6510 SEM (made in Japan). For pure TLM, PEG 4000, PVP K 25, physical mixing, and SD-formulation, scanning electron microscopy was used [32, 33].

Stability studies

Stability study is the most crucial evaluation component for the creation of a pharmaceutically effective product. Any dosage form's potential capacity to continue meeting the necessary physical, chemical, toxicological, and therapeutic requirements is referred to as its stability. SD formulation was charged at accelerated stability condition as per ICH i.e. 40±2 °C/75±5% RH condition for up to 3 mo in a stability chamber manufactured by Thermolab, and an assay of the formulation was determined [34-36].

Analytical method of dissolution profile comparison of SD formulation with marketed product

The optimized SD formulation was compared with the marketed formulation. Telmitan® 20 mg, (Nest Health Care Pvt Limited) for *in vitro* drug release using dissolution media–Phosphate buffer pH 7.5, USP II apparatus, the volume of media 900 ml, rpm-75, UV-296 nm. For comparative release profile assessment, both the similarity and

difference factors (F1) (F_2) were calculated as mentioned in the below equations:

$$F1 = \left\{\left[\sum_{t=1}^{n}|R_t - T_t|\right]\right\} \Big/ \left\{\left[\sum_{t=1}^{n} R_t\right]\right\} \times 100$$

$$F2 = 50 \times \log\left\{\left[(1 + 1/n)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

Where

R_t = Percent release for commercial formulations at various times (Reference product)

T_t = Percentage releases for different time points for SD formulation

n = The quantity of intervals in the drug release profile

Two formulations are considered to have similar profiles if the similarity factor (F2) is between 50 and 100 and the difference factor (F1) is between 0 and 15. The similarity factor (f2) indicates that the profiles of two formulations are different if it is less than 50 [37-39].

RESULTS

Characterization of the SD

Using a central composite design, a total of 20 different TLM SD formulations were prepared, with different concentrations of PEG 4000, PVP K25 and different stirring times. To determine the effectiveness on drug entrapping and drug release, all batches were subjected to analysis. Polynomial equations, contour plots, and 3D response plots were used to analyse the influence of variables on the responses. The effect of variables on both responses was discussed in table 2. For each response, the analysis of variance of test was used to determine the probability value (p). $p<0.05$ was regarded as the most significant level of probability.

Effect of variables on both the response

The linear model was found significant with an F value of 15.61, besides the effect of main variables was also determined. The p Value for model term A, B and C was found to be less than 0.05. In this case, all factors were significant and concentration of PEG 4000 was found highly significant.

Table 2: Central composite design TLM SDs using solvent evaporation technique

Formulation code	Run	Factor 1 A (PEG 4000) mg	Factor 2 B (PVP k25) mg	Factor 3 C (Stirring time) rpm	Response 1 Drug release*	Response 2 Entrapment efficiency (%)*
SD-1	1	20(-1)	180(+1)	300(+1)	78±0.6	84±0.3
SD-2	2	200(+1)	20 (-1)	100(-1)	85±0.8	88±0.2
SD-3	3	110 (0)	100 (0)	200(0)	86±0.5	87±0.7
SD-4	4	110 (0)	100 (0)	200(0)	86±0.3	88±0.5
SD-5	5	110 (0)	100 (0)	568(+1.68)	85±0.8	89±0.5
SD-6	6	200 (+1)	180 (+1)	300(+1)	95±0.4	98±1.1
SD-7	7	110 (0)	100 (0)	200(0)	87±0.6	89±0.4
SD-8	8	110 (0)	13.6 (-1.68)	200(0)	79±0.9	83±0.8
SD-9	9	336 (+1.68)	100 (0)	200(0)	95±0.7	99±0.8
SD-10	10	110 (0)	100 (0)	200(0)	86±0.6	88±0.5
SD-11	11	110 (0)	302.4 (1.68)	200(0)	86±0.5	91±0.7
SD-12	12	20 (-1)	20 (-1)	100(-1)	70±0.8	75±0.4
SD-13	13	20 (-1)	20(-1)	300(+1)	72±0.2	75±0.3
SD-14	14	13.6 (-1.68)	100 (0)	200(0)	75±0.6	79±0.9
SD-15	15	110 (0)	100 (0)	32(-1.68)	65±0.1	72±0.3
SD-16	16	200(+1)	180 (+1)	100(-1)	91±0.4	95±0.6
SD-17	17	20(-1)	180 (+1)	100(-1)	75±0.4	82±0.7
SD-18	18	200(+1)	20 (-1)	300(+1)	86±0.2	90±0.1
SD-19	19	110 (0)	100(0)	200(0)	88±0.3	92±0.8
SD-20	20	110 (0)	100 (0)	200(0)	85±0.4	88±0.6

*The results are presented in mean±SD (n=3)

Table 3: ANOVA table of regression (drug release and entrapment efficiency)

Source	Model type	Sum of Squares	Degree of freedom	Mean Square	F-value	p-value	Remarks
Y1	Linear	1041.14	3	347.05	15.61	<0.0001	Significant
Y2	2FI	919.15	6	153.19	35.19	<0.0001	Significant

Y1 = Drug release and Y2 = Entrapment efficiency

The polynomial equation of drug release in terms of actual factor is as follows.

Drug release =86.32+7.64*(A)+2.91*(B)+3.34*(C)+0.75*(A*B)+ 0.25*(B*C)+0.75*(B* C)+0.35*$(B)^2$-1.24*$(B)^2$-3.89$(C)^2$

Drug release equation demonstrated that PEG was having the greatest impact on the drug release as shown by its highest coefficient in the equation and least p-value. Fig. 2 demonstrates the effect of various variables on drug release. Concentration of polymers and RPM were having a significant impact on the drug release. Also, the diagnostic plot showed the normal distribution of studentized residuals.

Similarly, for entrapment efficiency 2FI model was found significant with F value of 35.19, besides, the effect of main variables was also determined. The p Value for model term A, B and C was found to be less than 0.05; in this case, all factors were significant.

The polynomial equation of drug release in terms of actual factor is as follows.

Entrapment efficiency =+65.23153+0.096807* A+0.083613* B+0.001454* C-0.000365 (A*B)+0.000014 (A*C)+0.000078 (B*C).

The above equations show that variables were having a significant impact on the response. Below fig. 2 demonstrates the effect of various variables on drug release and entrapment efficiency. Concentration of polymers and RPM were having a significant impact on both responses. Also, diagnostic plot showed the normal distribution of studentized residuals.

The effect of all three variables on the responses was studied through contour plots, 3D surface response plots and analysis of variance was also applied to study the significance of the model. The model was found significant for both responses as p Value is less than 0.05, which shows that factors selected have a significant impact on the response. A formulation which was having PEG 4000 (110 mg), PVP k25 (100 mg) and RPM (200) was considered an optimized formulation, as the relatively lesser amount of polymers significant release was achieved, SD formulations having code SD-3, SD-4, SD-7, SD-10, SD-19 and SD-20 were having this polymer and RPM combination. Further, SD-20 was taken as an optimized formulation.

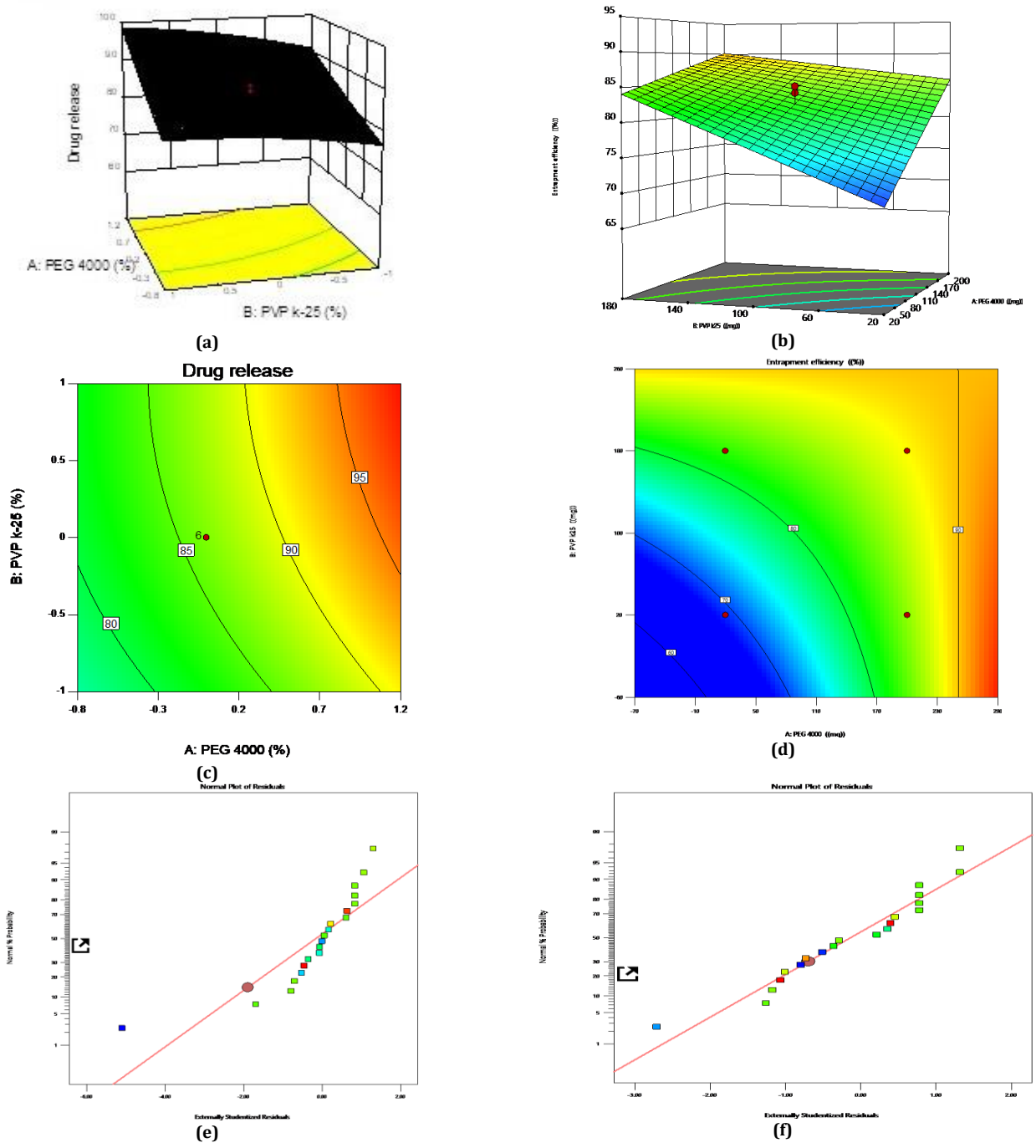

Fig. 2: 3D and contour plot of both responses (a) 3D plot response plot drug release (b) 3D plot response plot entrapment efficiency (c) Contour Plots for drug release (d) Contour Plots for entrapment efficiency (e) Diagnostic plot for drug release (f) Diagnosti c plot for entrapment efficiency

DSC studies

Due to its capacity to offer comprehensive details about a substance's physical and energetic properties, DSC may be defined as the thermal analysis method [25].

It is the most popular thermal approach for characterizing SD, it offers precise data on M. P., the transition temperature of the glass (Tg), and the generation and changes of energy connected to the transitions phase, which includes crystallization and union processes. Fig. 3 specifies the thermal analysis data of drug-polymer, PM, and optimised SD formulation.

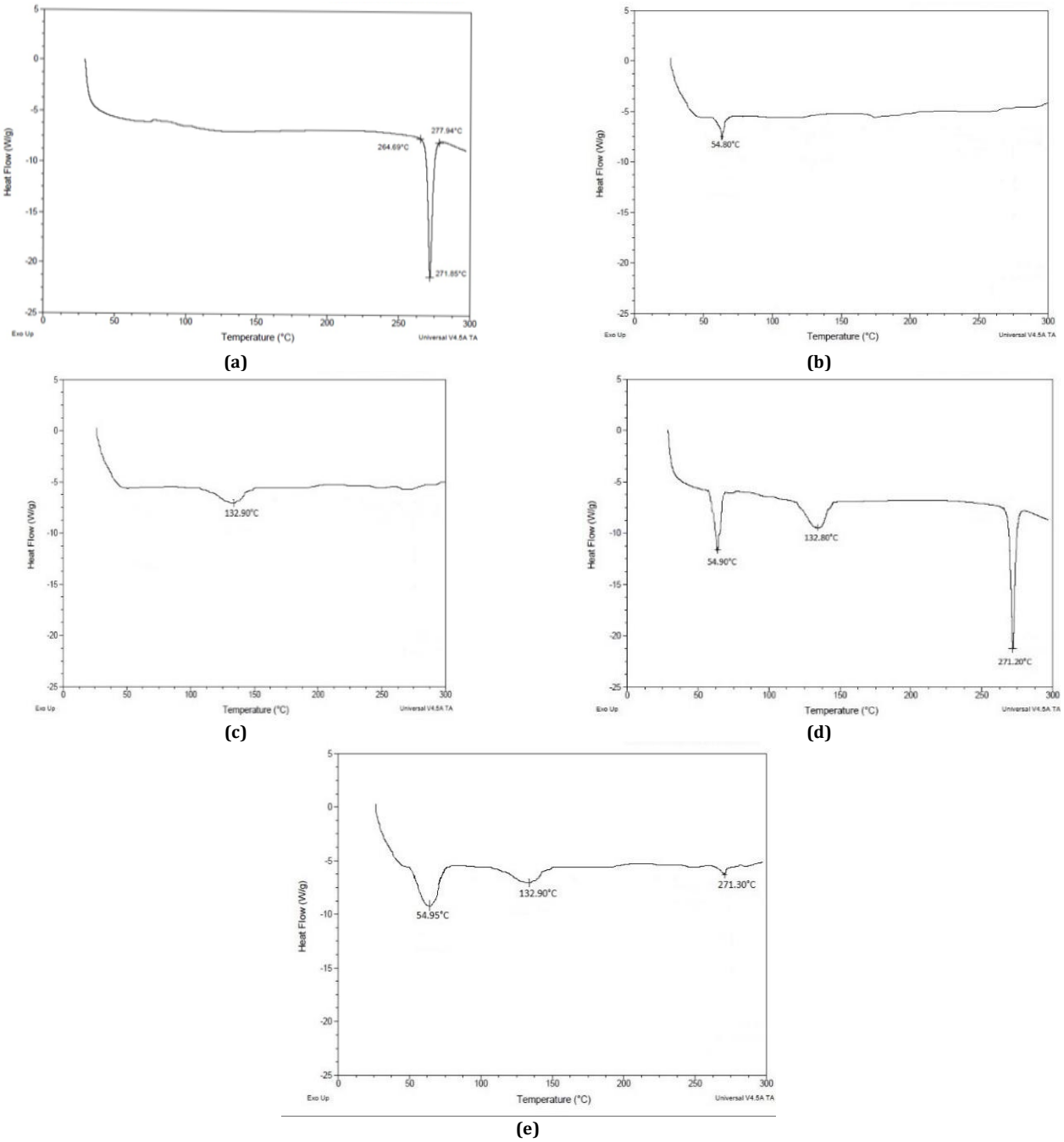

Fig. 3: DSC Thermograms of (a) Drug (b) PEG 4000 (c) PVP K25 (d) Physical mixture of drug and polymers (e) Optimised SD formulation

All TLM crystals were heated at that temperature, and no moisture was absorbed owing to the strong hydrophobicity of pure TLM, which displayed a sharp endothermic peak at 271.65 °C, which resembled its inherent melting point. PVP K25 and PEG 4000 both displayed an endothermic band that was relatively broad at 132.90 °C and 54.90 °C, respectively. DSC had also been performed for PM of drug and polymers and Optimized SD-formulation. Polymers showed no interference peak with API in PM, which confirmed the identification and compatibility between drug and selected polymers. In the DSC of SD formulation, the disappearance of the API peak reflected the changes in API after conversion into the formulation.

FT-IR studies

The identification of the drug and polymers was confirmed by the transitions of several functional groups in the IR spectra of the drug and polymers. FT-IR peaks of TLM showed characteristic peaks at 1690 cm^{-1}(C= stretching), 1301 cm^{-1}(C-N stretching), 1455 cm^{-1}(CH_3 bending) and 3135 cm^{-1}(OH-Stretching). IR spectra of PVP K 25 reflected the peaks at 1274 cm^{-1} (C-N stretching), 1658 cm^{-1}(C=O stretching) and 2945 cm^{-1}(C-H stretching) which confirmed the identity of polymer. Similarly, FTIR spectra of PEG 4000 showed characteristic peaks at 2878 cm^{-1} (methylene group), 1340 cm^{-1} and 1277 cm^{-1} (C-O stretching), 950 cm^{-1} (C-C stretching) and 838 cm^{-1} (C-H bending). IR Spectrogram of PM of drug and polymers was also assessed. It was showing no significant changes in the transition peaks which confirmed that there was no interaction of polymers with the drug and demonstrated the compatibility of drug and excipients. IR Spectrogram of formulation was showing changes that occurred in the transitions due to conversion of drug into SD formulations as shown in fig. 4.

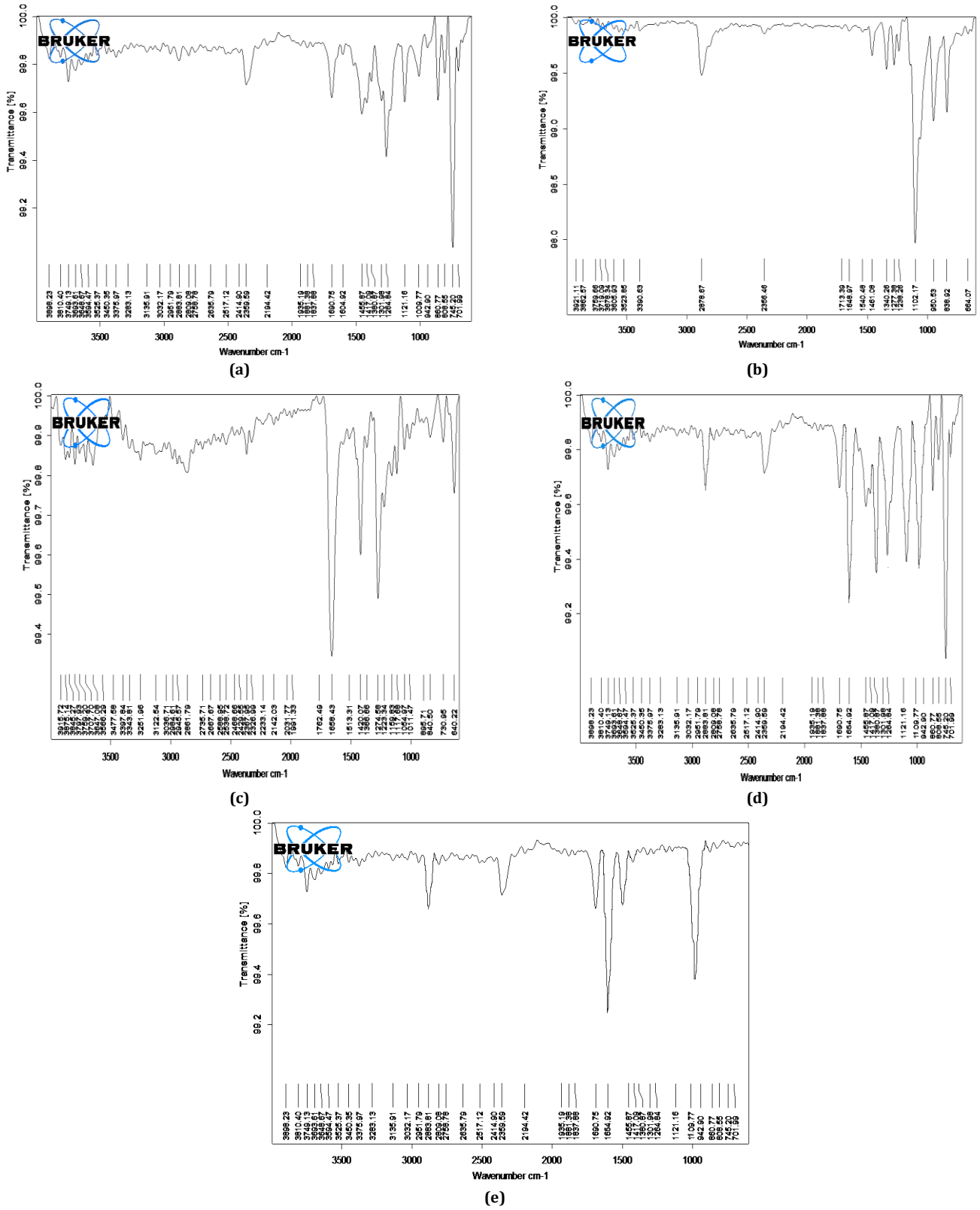

Fig. 4: IR spectrogram of (a) Drug (b) PEG 4000 (c) PVP K25 (d) Physical mixture of drug and polymers (e) Optimised SD formulation

XRD studies

XRD studies were performed for pure TLM, PEG 4000, PVP K 25, PM and SD formulation. Characteristic high-intensity peaks appeared in the XRD for TLM. The sharp XRD peaks of drugs indicated the crystalline nature, while polymers XRD were not having sharp peaks like drug indicating the less crystalline nature of polymers. XRD of PM reflected the compatibility between the drug and polymers. Further, after processing into the SD, instead of sharp characteristics peaks, flat curve was observed, which reflected the amorphous nature of formulation as shown in fig. 5.

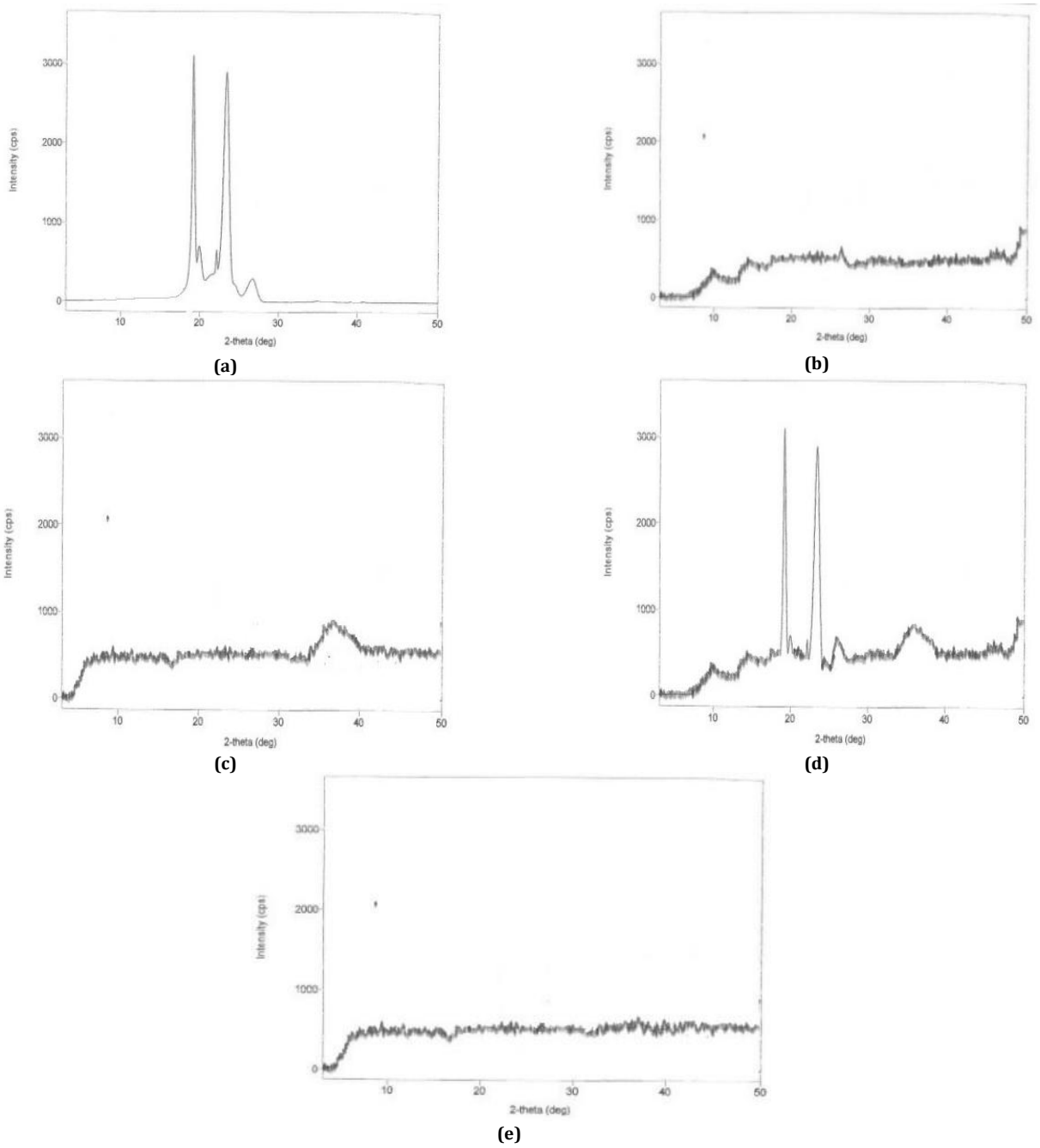

Fig. 5: XRD of (a) Drug (b) PVP K25 (c) PEG 4000 (d) Physical mixture of drug and polymers (e) Optimised SD formulation

Scanning electron microscopy

The morphological characteristics of TLM, PEG 4000, PVP K25, PM and Optimized SD-formulation were examined by SEM. SEM image of TLM showed small shaped irregular crystals. Additionally, the SEM images of PEG 4000 showed flat crystals of PEG 4000 with irregular edges, PVP K25 would show circular shaped round edges crystals, while the PM showed a mixture of all three. SD formulation showed the complete loss of structure of the drug and showed oozing waxy appearance. The waxy appearance reveals that the drug was completely enclosed in the polymer matrix. Fig. 6 shows the visual changes in drug and SD formulation. SD formulation indicated that changes happened with the drug after conversion in the form of SD formulation.

Stability studies

The optimised SD formulation was charged under accelerated stability conditions of 40 °C±2 °C/75%±5% Relative Humidity (RH) as per ICH condition. For stability assessment assay was determined at initial, 1 mo, 2 and 3 mo. No decreasing trend was observed in the assay over stability, which reflected no degradation of the main component. Assay value of SD formulation for initial time point was 98.64 % and for 3 mo 98.61 % was observed as given in table 4. No decrease in assay value depicted that the formulation was stable.

Table 4: Results of assay on various stability stations (n=3)

Time period (40 °C/75%RH)	Assay (%)
Initial	98.64±.0.08
1 Mo	98.44±0.23
2 Mo	98.42±0.34
3 Mo	98.61±0.41

*The results are presented in mean±SD (n=3)

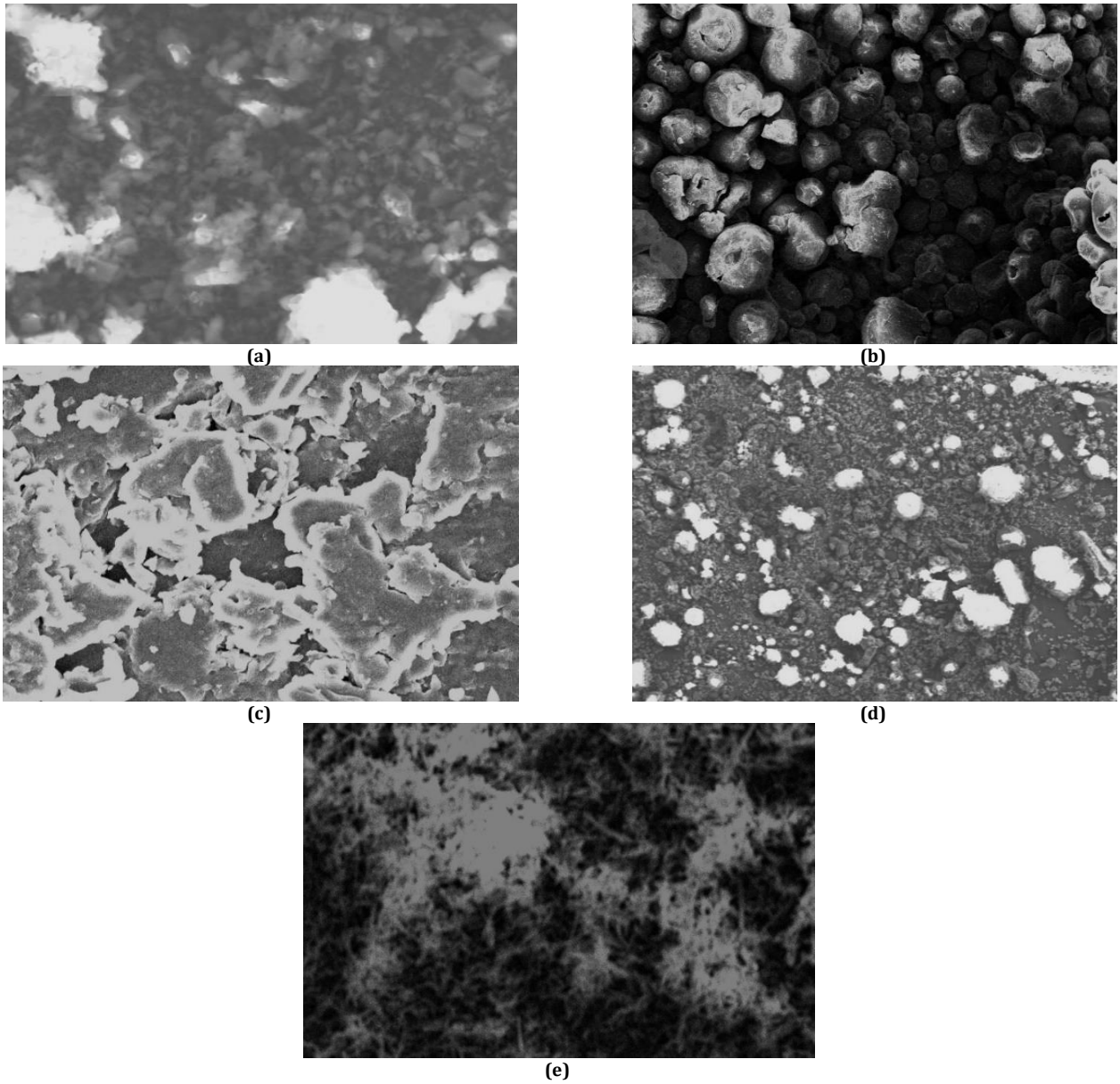

Fig. 6: SEM images (along with magnification) of (a) Drug (x140) (b) PVP K25 (x90) (c) PEG 4000 (x1500) (d) Physical mixture of drug and polymers(x30) (e) Optimised SD formulation (x270)

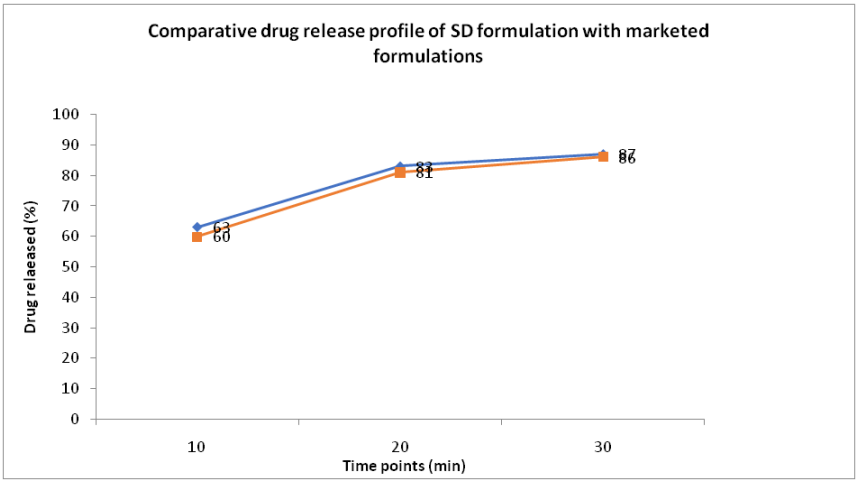

Fig. 7: Comparative drug release profile of SD-Formulation with the marketed product (n=3)

Comparison with marketed formulation

Dissolution profiles were compared with the marketed product (Telmitan 20 mg, Nest Health Care Pvt Limited), following data was observed. Drug release observed in SD formulation was similar to the marketed formulation, for both profiles, difference factor (F_1) and similarity factor (F_2) were calculated. If the similarity factor (F2) was between 50 and 100 and the difference factor (F1) was between 0 and 15, then two formulas' profiles are said to be similar. In the case of the aforementioned profile, the F2 value was 81 and the F1 value was 3. Hence both profiles were considered similar. Fig. 7 discusses the comparative drug release profile of SD formulation with marketed formulation.

Similar results were reported in the previously conducted study by Jalpairai *et al.*, 2020; Giri *et al.*, 2021 and Patel *et al.*, 2012 [40-42].

CONCLUSION

The formulation of the SD of TLM using a solvent evaporation method was found to be an effective and suitable method to improve drug dissolution. DoE was implemented with different concentrations of hydrophilic polymers PEG 4000 and PVP k25 at different rpm. Selected variables were found to have a significant impact on the responses (drug release and entrapment efficiency). Statistical analysis was performed on the results of DoE and found that variables selected were having a p-value less than 0.05% indicating that variables selected in the DoE study were having a significant impact on the selected responses. The optimized SD formulation was further characterized by FT-IR, DSC, XRD and which reflected the changes that occured in drug after conversion into the SD formulation. The drug was in the crystalline form after processing in SD, formulation resulted in amorphous nature. Polymers used in the trials increased the wettability of drug due to their hydrophilic nature which further improved the drug release. SD formulation was also found stable over accelerated conditions of stability as per ICH guidelines. Drug release profile study showed similar results as compared with the marketed product. So, it can be concluded that the specified ratio of polymers PEG 4000 and PVP K25 at specified rpm of stirrer were found to be effective to improve the drug release of TLM through SD technique.

ABBREVIATION

Solid dispersion-SD, Telmisartan-TLM, Polyethylene glycol 4000-PEG 4000, Polyvinylpyrrolidone K25-PVP K25, Rotation per minute-RPM, Design of experiment-DoE, Fourier-transform infrared spectroscopy-FT-IR, Differential scanning calorimetry-DSC, Scanning electron microscopy-SEM, X-ray diffraction-XRD, Phosphate buffer-PB, Physical mixture-PM, Relative humidity-RH

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Nil

AUTHORS CONTRIBUTIONS

Ritu Kaushik: Writing-Original Draft Preparation, Conceptualization; Ravinder Verma: Software, Writing-Review and Editing, Data Curation; Vikas Budhwar: Conceptualization; Deepak Kaushik: Conceptualization, Supervision. All authors have read and agreed to publish the manuscript.

CONFLICTS OF INTERESTS

Declared none

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