



Liquisolid Technique: a Novel Tool to Develop Aceclofenac-Loaded Eudragit L-100 and RS-100-Based Sustained Release Tablets

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Published online: 7 August 2020

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Abstract

Objective One of the main problems with NSAIDs is the dosing frequency, which leads to patients' noncompliance. To overcome this, fabrication of sustained release formulation of the drug is considered a well-reputed technique. The present study aimed to develop sustained release formulation of a model drug aceclofenac through the new liquisolid technique.

Methods Liquisolid powder prepared using glycerin as the liquid vehicle was subjected to pre-compression evaluation, including bulk and tapped densities, Carr's compressibility index, Hausner's ratio, angle of slide, FTIR, and atomic force microscopy (AFM). Differential scanning calorimetry (DSC) and X-ray crystallography studies were investigated for any complex formation between drug and excipients, as well as crystal form alterations during the manufacturing process. Powders were compressed into tablets and quality control tests; in vitro dissolution test and storage stability studies were carried out.

Results The release of aceclofenac was at a predetermined rate and followed zero-order kinetic models. AFM confirmed the surface morphology and particles were well adsorbed by the carrier material. FTIR and DSC studies suggested no drug–excipients interaction and the drugs were found in an amorphous form, which was confirmed through XRD. Upon storage at the given conditions of humidity and temperature, the formulation was found stable.

Conclusion The study proved that liquisolid technique can be used successfully to develop a sustained release formulation.

Keywords Aceclofenac · Liquisolid technique · Sustained release formulation · Drug release kinetics · Stability

Introduction

Liquisolid technique is a novel promising technique that involves the incorporation of drug solution, drug suspension or oily drug directly in non-volatile, water-miscible and inert solvents (–propylene glycol, polyethylene glycol, Tween-80 and glycerin) into a specified quantity of carrier and coating materials that results in a production of freely-flow able, non-adhesive and readily compressible powders [1]. When carrier material with high absorption capability and surface area is wetted by non-volatile water miscible solvent, it results in the production of powder having less flow ability, so coating materials (polymers) having excessive fine particles and high surface area are incorporated into it. Thus the resultant powder becomes readily flow able and compressible [2]. The formulation of Liquisolid compacts is also dependent upon the choice of solvent used. If the drug is more soluble in a solvent it will enhance the dissolution rate and ultimately the bioavailability of the drug, whereas if a drug is least soluble in a solvent it will result in the retardation of or sustaining drug release [3].

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All those patients suffering from any type of arthritis need chronic therapy for a long time with intermittent administration of the drug. Due to the shorter biological half-lives of such drugs, the continuous administration results in poor patient compliance [4]. Aceclofenac due to its multi dosing schedule (i.e. 100 mg bid) and shorter half-life of 4 h [5] make it fit candidate for sustained release formulation [6]. Aceclofenac (AC) is an analgesic anti-inflammatory drug that belongs to NSAIDs. It is used to treat osteoarthritis, arthritis, rheumatoid arthritis, and ankylosing spondylitis [7]. Inflammation, pain, and pyrexia are mainly induced in the body by a specific mediator - prostaglandin. Aceclofenac irreversibly inhibits synthesis of prostaglandin by inhibiting the cyclooxygenase enzyme. Specifically inhibit cyclooxygenase pathway results in prostaglandin synthesis irreversibly [8]. Additionally, when Aceclofenac is formulated in a sustained release form, it will result in avoiding unwanted side effects concerned with Aceclofenac because the bursting effect will be avoided responsible for more side effects [9].

The rationale of the study is that the conventional coating for sustained release formulation is a cost effective and time-consuming process. Because it needs an additional coating step, extra labor and machinery cost, whereas, the liquisolid technique bypasses such additional process. Eudragit L-100 and Eudragit RS-100 were evaluated, because these are hydrophobic in nature and polymers of choice according to the theory of liquisolid technique [10]. These polymers are choices because these are hydrophobic in nature with low surface area, so are suitable for sustain release formulation (retains the drug for long period of time).

Materials and Methods

Aceclofenac (Amoli Organic private limited, India), Aceclofenac reference standard was gifted by NAVÉGAL laboratories, Hattar Industrial Estate, Haripur Pakistan). Methacrylic acid (Eudragit L-100 and RS-100) and colloidal silicon dioxide (Aerosil –200) were purchased from Laurel Asia trading (SDN BHD 47100 Puchong Darul Ehsan Malaysia). Glycerin, phosphate buffer/potassium phosphate monobasic (Duksan pure, KOREA), sodium hydroxide pellets (Merck KGaA, EMD Millipore Corporation, Germany), Tween-80, PEG 200 and 400 were of analytical grade.

Formulation Design of Liquisolid Compacts through Use of Mathematical Model

The liquisolid compacts were formulated according to the theory and mathematical model presented by Spirease [11]. According to this model, glycerin was used as a liquid vehicle

based on its drug solubility, Eudragit L-100, and RS-100 were separately used as carrier materials and Aerosil-200 was used as a coating material.

According to the theory of liquisolid system carrier and coating material retain a specified quantity of liquid vehicle that ensures acceptable flowability and compressibility. The ratio of carrier to coating material is termed as excipient ratio of powder (R), defined as,

$$R = \frac{Q}{q} \quad (1)$$

Where R is excipients ratio, Q is carrier material weight and q is the weight of coating material used in the formulation.

Load factor (L_f) is the ratio between the weight of liquid medication (drug dissolved or dispersed within the liquid vehicle) over weight of carrier material used that produces a powder with acceptable flowability and efficient compression.

$$L_f = \frac{W}{Q} \quad (2)$$

Where W is the weight of liquid medication and Q is the weight of carrier material. The load factor was further used for the determination of carrier and coating material quantity.

Solubility Studies

Excess quantity of Aceclofenac was added to glycerin, Tween-80, polyethylene glycol grade 200, 400 and propylene glycol separately. The resultant saturated solutions were shaken in a vortex shaker (SCIOLOGEX MX-F) for 36 h. The solutions were then centrifuged for 2 h at 4000 rpm and the supernatant was filtered, diluted and observed through UV-spectrophotometer (IRMECO model U-2020) at a scanning λ of 276 nm. Drug solubility in each liquid vehicle was determined [12].

Calibration Curve Using HPLC Method

An accurately weighed 30 mg of Aceclofenac was transferred to 100 ml volumetric flask and diluted with 100 ml phosphate buffer pH 7.5, so having a known concentration of 300 $\mu\text{g/ml}$ (stock solution). A series dilution ranging from 0.25–50 $\mu\text{g/ml}$ was prepared from stock solution using the same dilution solvent. A volume of 20 μL of each dilution of series was injected to HPLC (Shimadzu, model SPD-15C, Japan), using triethylamine: acetonitrile: (85:15 v/v) containing 2 ml triethyl amine as mobile phase. The flow rate was maintained at 1 ml/min with detecting lambda of 275 nm. The results obtained were used in constructing the calibration curve.

Determination of Flowable Liquid Retention Potential (\emptyset -Value) and Angle of Slide

Flowable liquid retention potential (\emptyset -value) for both carrier and coating materials is defined as the maximum quantity of liquid vehicle entrapped (w/w) within excipients by maintaining acceptable flowability. An accurately weighed 25 g of the carrier material (Eudragit L-100 and RS-100), coating material (Aerosil-200) and the liquid vehicle was taken and mixed in a mortar with the help of pestle. The resultant blend of powder was sieved (1 mm mesh size sieve) and homogenized. The blend was observed each time for the angle of slide by taking 10 g from the admixture, kept on the surface of the smooth metal piece and tilted gradually until the powder starts to flow downward. At this stage, the angle of a metal piece with the horizontal surface was determined [13]. The optimum and acceptable range of angle of slide for the lquisolid system is 33° [14]. When the angle of slide was exceeded than normal (33°), at each step of the process, it was tuned in term of powder excipients or liquid vehicle. \emptyset -value for carrier material and coating material was calculated as liquid to mass ratio of the admixture with angle of slide corresponding to 33° using the following equation.

$$\emptyset\text{-value} = \frac{\text{weight of liquid vehicle}}{\text{weight of carrier/coating}} \quad (3)$$

Preparation of Aceclofenac Sustained Release Powder and Compression Thereof

An accurately weighed quantity of liquid vehicle (glycerin) was heated to 80°C and the weighed quantity of the drug was introduced in a 100 ml glass beaker. The formed liquid medication was transferred into a mortar and the calculated quantity of carrier material was added. The produced wet mass was stirred, spread over the surface of mortar and kept undisturbed for 10 min to completely absorb the liquid medication. The crispy layer was scratched from the mortar wall and coating material was incorporated and triturated thoroughly, via pestle until non-adherent, free-flowing and the readily compressible powder was achieved [15]. Other necessary excipients were introduced and the powder was compressed into tablets in 18 mm oblong shape punch using a rotary compression machine (Zp-17 compression machine) with sufficient compression force to produce tablets with a hardness of $4\text{--}7\text{ kg/cm}^2$ (Table 1).

Code T “formulation with Eudragit L-100”, Code S “formulation with Eudragit RS-100”, R-value is excipients ratio (ratio of carrier to coating material), L_f is load factor (ratio of liquid medication to carrier material weight), Drug (Aceclofenac), Solvent (Glycerin), L-100 (Eudragit L-100 as a carrier material), RS-100 (Eudragit RS-100 as a carrier

material), Aerosil –200 (colloidal silicon dioxide as a coating material).

Pre-Compression Characterization

Flow Properties Evaluation

Powder flow is of prime importance at the industrial level because it ensures efficient compression. In current research work, basic flow ability parameters were evaluated including Carr’s compressibility index and Hausner’s ratio. Bulk and tapped densities were determined by taking a suitable quantity of powder in the graduated cylinder and volume occupied before and after tapping were observed. Carr’s compressibility index was determined using the following formula [16].

$$CI\% = \frac{P_t - P_b}{P_t} \times 100 \quad (4)$$

Where P_t tapped density and P_b is bulk density.

British Pharmacopeia (BP) categorize the CI % less than 25 in an acceptable range of flow properties [17]. Whereas Hausner’s ratio was calculated by dividing the tapped density value over bulk density [18]. The angle of repose was determined using the fixed funnel method [19]. The funnel was fixed at a suitable height, the powder was allowed to fall through funnel orifice which forms a heap with a horizontal surface. The angle of repose (α) was determined by employing the following formula.

$$\alpha = \tan^{-1} (2h/r) \quad (5)$$

Where h is pile height and r is the distance between the pile center and edge.

Differential Scanning Calorimetry (DSC)

An accurately weighed 2 mg of lquisolid powder was sealed tightly in the aluminum pan against an empty aluminum pan as the reference standard. The DSC (TA instrument model 2010, the USA) measurements were carried out at a scanning rate of $10^\circ\text{C}/\text{min}$ and a temperature range between 0 and 350°C .

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR studies were conducted to check out drug-excipients interaction. The sustained release lquisolid formulation, carrier material, coating material; physical mixture and active drug were analyzed using IR spectrophotometer (Shimadzu, Kyoto, Japan). The method adopted was the KBr disc method at a scanning time of 3 min. The spectra were recorded at a scanning range of (4000 cm^{-1} and 400 cm^{-1}). The recorded

Table 1 Formulation design of aceclofenac liquisolid sustained release tablets

Trial #	R-value	L_f	Drug (mg)	Solvent (mg)	L-100 (mg)	RS-100 (mg)	Aerosil (mg)	Mg stearate (mg)	Weight (mg)
T1	2.86	0.58	100	150	430	–	150	10	840
T2	3.91	0.53	100	150	470	–	120	10	850
T3	6.25	0.5	100	150	500	–	80	10	840
S1	2.86	0.58	100	150	–	430	150	10	840
S2	3.91	0.53	100	150	–	470	120	10	850
S3	6.25	0.50	100	150	–	500	80	10	840

Code T “formulation with Eudragit L-100”; code S “formulation with Eudragit RS-100”; R-value is the excipient ratio (ratio of carrier to coating material); L_f is the load factor (ratio of liquid medication to carrier material weight); drug (aceclofenac); solvent (glycerin); L-100 (Eudragit L-100 as a carrier material); RS-100 (Eudragit RS-100 as a carrier material); Aerosil-200 (colloidal silicon dioxide as a coating material)

spectra were evaluated and compared for any spectral changes.

X-Ray Crystallography (XRD)

To investigate the crystallinity alteration, Powder X-ray diffraction patterns of liquisolid powder, physical mixture, and pure Aceclofenac were carried out using (PANalytical’s XPERT-PRO diffractometer system), using Cu, $K\alpha$ and $K\beta$ radiations, (45 kV, 40 mA and 25 °C). The powder samples were analyzed between 2θ angles ranging from 5 to 40°. The recorded diffractograms were compared for their chemical composition and crystal habit.

Atomic Force Microscopy (AFM)

Atomic force microscopic study (AFM) was carried out for visualization of particles and morphology. Powder samples were suspended in distilled water, dropped on mica slide, dried in a dust-free environment and then visualized under AFM (5500, Agilent technologies; USA) in the non-contact mood.

Post-Compression Evaluation

Physical in-Process Characterization

Hardness test was performed on six tablets from each batch using a digital hardness tester model (Rockwell 900–365). Friability test was performed on ten tablets using friabilater model (FB-0498 ‘CURIO) and percent loss was determined [20]. For content uniformity six tablets from each trial were evaluated, tablets should contain 90–110% contents corresponding to its label claim [21]. Weight variation test was conducted on ten tablets, individual weight and then mean weight was determined. Tablets were evaluated in their sanctioned pragmatic limit [22].

In Vitro Dissolution Test

The dissolution test was employed for ensuring the sustained release of the drug. The prepared tablets were run for two hours in simulated gastric fluid in dissolution apparatus (HCl with pH 1.2 at 37 °C). The dissolution process for Diclofenac sodium as per USP was taken as a model method. USP paddle apparatus was used containing 900 ml of phosphate buffer (0.05 M, pH 7.5), adjusted at temperature 37 °C and paddle speed of 50 RPM. Samples were withdrawn at an interval of 1,2,4,6,8,12 h respectively and observed through HPLC. The concentration was calculated from the regression equation of the calibration curve.

Dissolution Data Analysis in Term of Kinetic Model

Dissolution results obtained were fitted into various kinetic models to elaborate the mechanism and drug release kinetics. These models include the first-order model, zero-order release model [23], Higuchi model [24], Korsmeyer Peppas model [25] and Hixson Crowell model [26]. The values of the regression coefficient (r^2) obtained from the kinetic release models were compared for the best fit model.

Stability Studies

Stability studies were carried out according to the ICH guideline, for 6 months (accelerated stability), at 40 ± 2 °C and 75% RH \pm 5% [27] in the stability chamber LABTRON model STCL-400. Aging studies were conducted for trial T3 because of the most reliable sustained release of the drug. Tablets were assessed for dissolution to check the aging effect upon storage following humidity and temperature.

Statistical Analysis

Statistical analysis, graphs, and tables design were carried out using, GraphPad prism 7 and Excel 2013.

Results and Discussions

It is investigated that liquisolid technique can be adopted as a promising tool to prepare sustained release formulation with the interest of achieving zero-order release kinetics [28]. The main aim of the current research work is to formulate Aceclofenac under the liquisolid technique, having a biological half-life of 4 h and multi dosing schedule drug, thus presenting it as a fit candidate for sustained release formulation.

Solubility Studies

To investigate the best liquid vehicle for current research work, the solubility of Aceclofenac was determined. The solubility of Aceclofenac in polyethylene glycol (PEG-400), polyethylene glycol (PEG-200) propylene glycol (PG), polysorbate (Tween-80) and glycerin was 15.93 µg/ml, 16.4 µg/ml, 11.91 µg/ml, 6.07 µg/ml and 2.98 µg/ml, sequentially (Table 2). The selection of a suitable solvent was based on its solubility i.e. solvent with least drug solubility was assumed to be used for sustained release formulation [29]. Glycerin was exploited as a nonvolatile liquid vehicle for Aceclofenac liquisolid sustained release system as the drug was least soluble in glycerin.

Calibration Curve

Calibration curve (Fig. 1). of Aceclofenac in phosphate buffer pH 7.5 manifests maximum absorption at 275 nm and retention time of around 5.5 min, so it was used as the analytical wavelength and retention time. The regression equation was $y = 0.9578.9x - 1184.9$ with correlation coefficient 0.999. Both these values significantly confer the exhibition of a linear relationship amid drug concentration and absorbance.

Ø-Value and Angle of Slide

Flow features of liquisolid admixture are based on the angle of slide. Liquisolid blends with 33° angle of slide are acceptable in terms of powder flow and eventually compression. Initially, the angle of slide was too high (83°) due to the higher quantity of liquid vehicle. The

Table 2 Solubility of aceclofenac in various non-volatile solvents

Solvent	Solubility (µg/ml)
PEG-200	16.4
PEG-400	15.93
PG	11.91
Tween-80	6.07
Glycerin	2.98

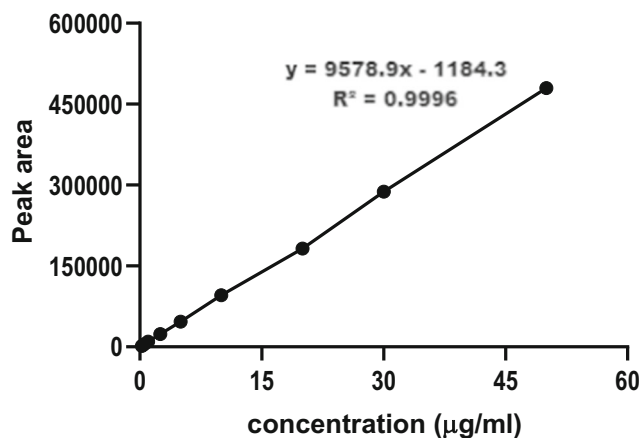


Fig. 1 Calibration curve

resultant blend was in the form of wet mass. It can be explained by the fact that carrier /coating material particles were saturated and the excess quantity of liquid vehicle ooze out from admixture that hinders the powder flow. But as the quantity of liquid vehicle was reduced the angle of slide was reduced too, until it reaches the optimal range (83°). The plot of the relationship between the angle of slide versus Ø-value of carrier /coating material is shown in (Fig. 2).

Flowable liquid retention potential (Ø-value) also help in formulation design i.e. how much carrier/coating material will be required and how much liquid vehicle will be sufficient to produce a powder with acceptable flowability and compressibility. The flowable liquid retention potential value for carrier material was 0.20 and 1 for the coating material. Both values are lower, thus helped in low weight tablets – because the employed solvent was well absorbed by lesser quantity of these excipients. So, low quantities of these polymers owed toward reducing the bulk of formulated tablets.

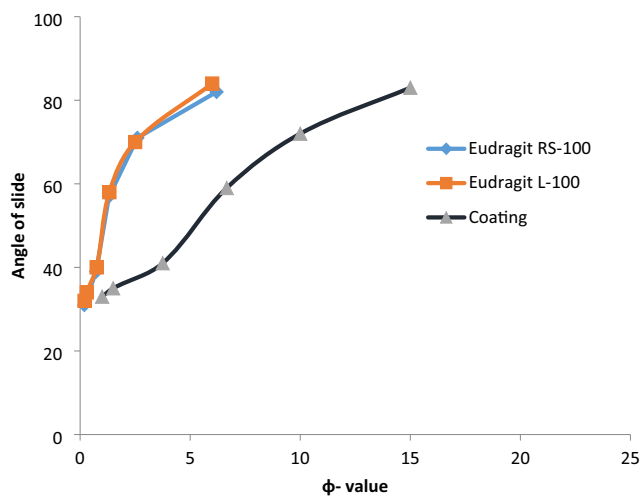


Fig. 2 Flowable liquid retention potential versus angle of slide

Preparation of Sustained Release Lisiquid Powder

Acceclofenac was picked as a model drug for sustained release formulation. The liguosolid powder was prepared based on flowable liquid retention potential value of carrier and coating materials. A binary mixture of Eudragit L-100 coded as (T1, T2, T3), Eudragit RS- 100 denoted as (S1, S2, S3) being carrier material and Aerosil-200 being coating material were introduced to liquid medication. According to the spirease theory, when drug solution, suspension or oily drug is incorporated into a carrier material with penetrable structure and closely packed fibers, the drug adsorbs on the recess of carrier material particles. When saturation of carrier occurs, the excess drug particles adsorb to the interior and exterior of the carrier material [30]. Then the excess drug particles are adsorbed by coating material (Aerosil-200) with high absorptivity and specific surface area, thus conduce to produce free-flowing, readily compressible, non-adherent and non-sticky powder [31]. All the formulations showed good flow behaviors (Table 3). The sustained release tablets of Aceclofenac were manufactured through direct compression. The pre-compression mingle was characterized for bulk density, tapped density, carr's compressibility index, angle of repose, and Hausner's ratio. Results obtained indicating good flowability, compressibility and are shown in (Table 3). For all trials, the R-value (excipient ratio) ranges between 2.86 to 6.25. Excipient's ratio is a very significant determinant in the liguosolid system because it has a great influence on drug release (detail in, in vitro dissolution section). An inverse relation was found between the excipients ratio and load factor because increasing the quantity of carrier material, decreases the quantity of liquid vehicle.

Pre-Compression Characterization

Flow Behaviors

For the production of powder with promptly flow, the load factor must not exceed over excipients than the optimal range. Because in doing so, powder with wet nature is produced which is powerless to flow. The Carr's index was evaluated

for liguosolid powder which has an indirect relation with powder flow and cohesiveness. British pharmacopeia admits those powders in an admissible range owning Carr's index less than 25% [17]. Whereas in the current study the value of Carr's index for all optimal trials ranges from 8.0 to 12.0%, that also comply with USP criteria (< 15%) [32]. The lower values of Carr's index for liguosolid powder are attributed to the presence of colloidal silica that has a more specific surface area ($201 \pm 7 \text{ m}^2/\text{g}$) and thus assures efficient flow characteristics. The Hausner's ratio ranges from 1.09 to 1.13, while the angle of repose ranges from 25° to 27° (< 40°), both parameter values indicate, that all the formulations lie within the excellent category of powder flow and exhibit non-cohesive nature. The flow characteristics are shown in Table 3.

Differential Scanning Calorimetry (DSC)

DSC studies were carried out to examine the physical state as well as the interacting status of Aceclofenac in liguosolid formulation. DSC thermogram of pure drug, physical mixture and optimized formulation is shown in (Fig. 3). The active drug, optimized formulation and physical mixture show endothermic peaks at approximately 155.53°C , 147.89°C , and 153.12°C , corresponding to the melting transition point of Aceclofenac. However, the endothermic peak of optimized formulation was found wider as compared to the pure drug, indicating the existence of the drug in an amorphous and molecularly dispersed state within the liquid vehicle owing to its higher dissolution (89%). The higher drug release was sustained by the maximum quantity of polymer in the optimized formulation as corresponded to other formulations. The absence of additional peaks from the powder of optimized formulation also proves the stability of Aceclofenac within the formulation and ensure the drug–excipients compatibility.

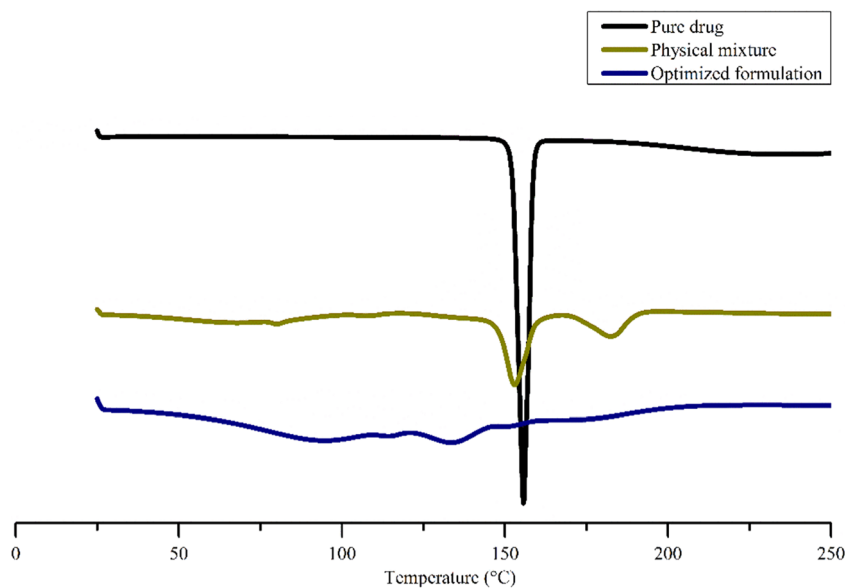
Fourier Transform Infrared Spectroscopy (FTIR)

An infra-red analysis is a rapid and handy tool for the measurement of bonds' vibrations within different functional groups. FTIR studies were conducted for sustained release liguosolid formulation, pure active drug (Aceclofenac) and

Table 3 Flow characteristics of prepared liguosolid sustained release powder (mean \pm SD, $n = 3$)

Trial #	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (°)
T1	0.357 ± 0.001	0.398 ± 0.003	10.29 ± 0.69	1.11 ± 0.01	25.82 ± 0.67
T2	0.364 ± 0.002	0.395 ± 0.003	08.61 ± 0.45	1.09 ± 0.01	25.25 ± 081
T3	0.367 ± 0.002	0.400 ± 0.003	08.32 ± 0.96	1.09 ± 0.02	26.02 ± 0.78
S1	0.345 ± 0.002	0.392 ± 0.003	11.99 ± 1.08	1.13 ± 0.02	27.55 ± 0.79
S2	0.350 ± 0.001	0.396 ± 0.002	11.77 ± 0.34	1.13 ± 0.01	27.57 ± 1.02
S3	0.351 ± 0.003	0.396 ± 0.003	11.51 ± 1.32	1.13 ± 0.02	26.80 ± 0.57

Fig. 3 Differential scanning calorimetry (DSC) of pure drug, physical mixture, and optimized formulation (T3)



other formulation constituents individually to confirm the integrity of active drug in both formulations and point out possible drug–excipients interactions. The FTIR spectra are shown in (Fig. 4). The FTIR spectrum of Aceclofenac shows the principal peak at 3318 cm^{-1} because of aromatic C-H stretching vibrations and 2931 cm^{-1} due to aliphatic C-H stretching vibrations, a band at 1713 cm^{-1} because of C=O stretching, a sharp band at 1775 cm^{-1} was observed due to C=O stretching of carboxylic acid, a band at 3364 cm^{-1} due to N-H rocking vibrations. A sharp peak was observed at 727 cm^{-1} due to 1, 2 di substituted C-Cl stretching. In the case of aerosil, the spectra reveal an absorption band at 3443 cm^{-1} , which might be attributed to the OH group resulting from

intermolecular hydrogen bonding between water and oxygen present in silica (SiO_2). A small band at 1643 cm^{-1} corresponds to H-O-H bending of water (moisture). An asymmetric stretching vibration for Si-O was observed at 1107 cm^{-1} which corresponds to the asymmetric Si-O stretching and bending modes of silica being recorded at 804 cm^{-1} and 471 cm^{-1} . The principal peaks for Eudragit L-100 were observed at 1045 cm^{-1} , 642 cm^{-1} , 2915 cm^{-1} and 3428 cm^{-1} due to C=O stretching vibrations, CH-OH stretching vibrations, aliphatic OH stretching and for OH group, respectively. In the case of optimized formulation (T3), the characteristic peaks of Aceclofenac were also clearly appeared in the spectra of the physical mixture and liquid formulation

Fig. 4 FTIR studies of drug, Aerosil, L-100, physical mixture, and optimized formulation (T3)

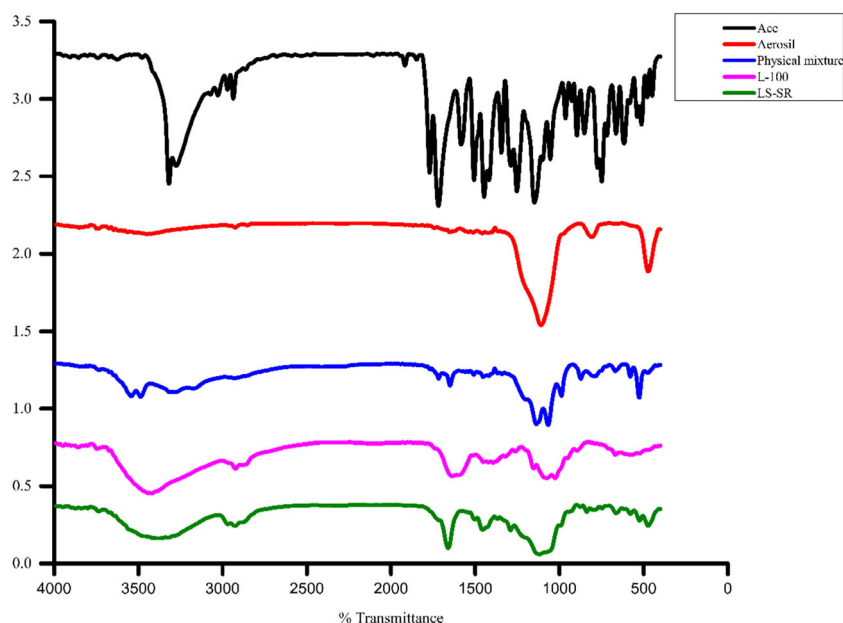
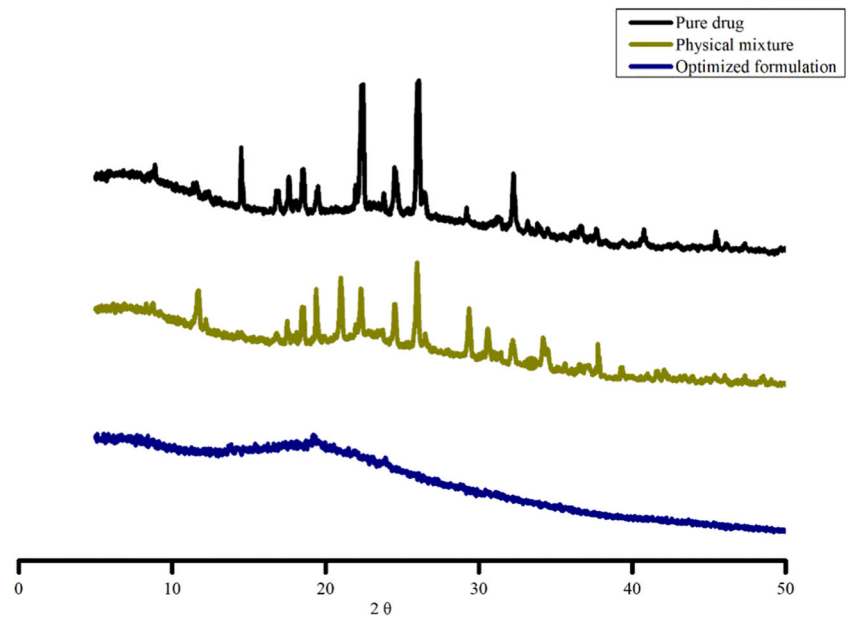


Fig. 5 X-ray crystallography (XRD) of drug, physical mixture, and optimized formulation (T3)



without any shifting of peaks. This lack of peaks alterations and absence of peaks shifting effectively indicates the absence of any chemical interaction between drug and excipients in the optimized formulation.

X-Ray Diffraction

The x-ray diffractogram of pure drug, physical mixture and optimized formulation is shown in (Fig. 5). The characteristic diffractogram of the pure drug was observed at 13° , 17° , 22° , 28° and 32° at 2θ . The permanence of such distinctive peaks confirms the crystal form of pure drug. In the case of the physical mixture, the diffractogram clearly shows the presence of pure drug distinctive peaks, however with a rebate in intensity up to some extent. This might be attributed to the

uptake of moisture by excipients that reduce the crystallinity was observed in the physical mixture. These distinctive peaks were lost in the optimized formulation. Moreover, the absence of distinctive peaks in the optimized formulation indicates the existence of the drug in the molecularly dispersed state (Aceclofenac in glycerin) or amorphous form. This is the beauty of the liquisolid technique that sustains the release of the drug being in amorphous form (enhance dissolution), so it can be used as an active tool for dissolution rate enhancement as well as sustained release formulation.

Atomic Force Microscopy (AFM)

The AFM study confirmed the surface morphology of optimized formulation. The physical image is shown in (Fig. 6).

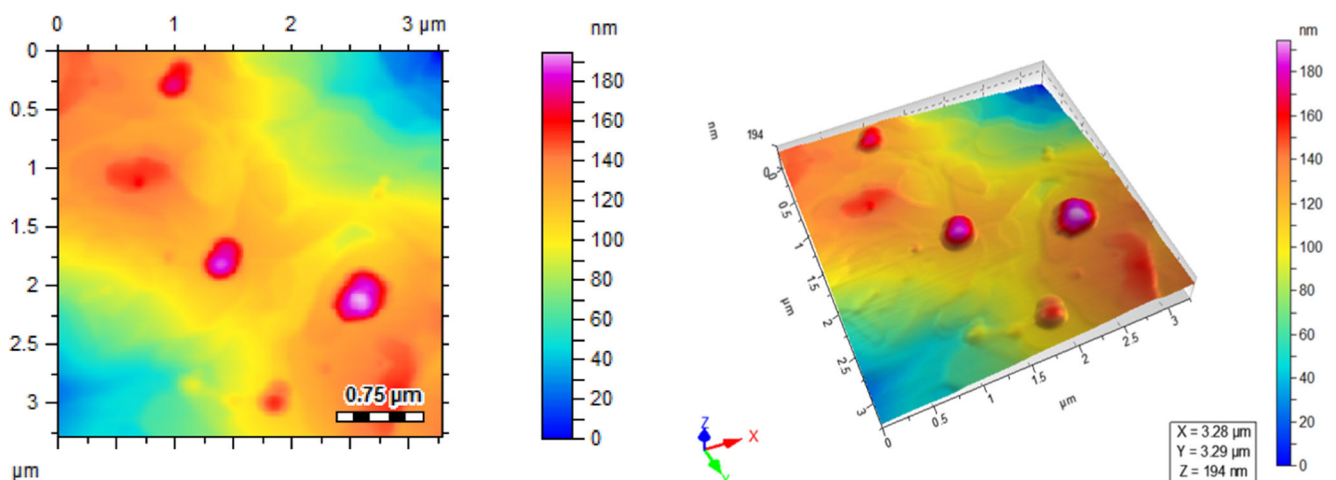


Fig. 6 Atomic force microscopy (AFM) of optimized formulation (T3)

Table 4 Physical in-process of compressed liquisolid sustained release tablets (mean ± SD)

Trial #	Hardness (kg/cm ²) ^a	Friability (%) ^b	Content uniformity (%) ^c	Weight variation (%) ^d
T1	4.83 ± 0.03	0.1	99.87 ± 0.08	± 1%
T2	4.82 ± 0.04	0.43	99.86 ± 0.09	± 1%
T3	5.09 ± 0.04	0.27	99.40 ± 0.66	± 1%
S1	4.91 ± 0.03	0.21	99.20 ± 1.05	± 1%
S2	6.09 ± 0.04	0.17	99.87 ± 0.22	± 1%
S3	5.47 ± 0.04	0.33	99.87 ± 0.09	± 1%

^a Equals 6

^b Equals 10

^c Equals 6

^d Equals 10

Particles were spherical and were absorbed efficiently by carrier material. The covering of all surfaces was homogeneous.

Post-Compression Evaluation

Physical in-Process Evaluation

All the prepared liquisolid sustained release tablets were evaluated for physical in-process parameters. The results are shown in (Table 4). The mean hardness values of tablets were between 4 and 6 kg / cm². At this hardness range, the tablets were capable to remain stable within dissolution media. The percent loss was between 0.1 and 0.4% (not more than 1%) and the tablets were able to confront mechanical abrasion as well as can easily be blistered, packaged and shipped. All the prepared tablets comply with the weight variation test (±3%). Drug content was from 99.20 to 99.87% that ensures consistent distribution of contents within each core and ensures efficient mixing process. All the physical in-process tests employed to liquisolid sustained release tablets substantially comply with the official standard specifications.

In Vitro Dissolution Test

Drug Release from Liquisolid Sustained Release Tablets Containing Eudragit L-100

The in-vitro drug release studies were carried out in both acidic (pH 1.2) and basic media (pH 7.5) for Eudragit L-100 based tablets. Drug release data is shown in (Fig. 7). The drug release from all trials in acidic media was < 10% whereas in basic media the drug release was 23.60 ± 0.25%, 21.90 ± 0.19%, 15.50 ± 0.14% after 1 h and 92.90 ± 0.14%, 92.50 ± 0.14% and 88.90 ± 0.09% till the end of 12 h, respectively for trial T1, T2 and T3. It is clear from Table 5 that correlation coefficient values (r²) of respective trials for zero-order release kinetics were higher than r² values for first-order release

kinetics (0.947, 0.951 and 0.980 > 0.944, 0.948 and 0.947). it clearly indicates that the formulated sustained release tablets of Aceclofenac follow zero-order release kinetics. Hixon Crowell model is based on drug release from a system due to change in surface and diameter of the particle [33]. The r² values of the Hixon Crowell model for trial T1, T2 and T3 were 0.969, 0.972 and 0.983, respectively. These values indicate, that drug in sustained release tablets is in a molecularly dispersed form (reduced particle size). The model also encourages the cylindrical shape of tablets. Higuchi model is based on a release from porous compacts. The r² values of T1, T2, and T3 for the Higuchi model were 0.962, 0.962 and 0.969, respectively. These higher values confirm the release of drug from liquisolid compacts through diffusion mechanism [34].

Drug Release from Eudragit RS-100 Based Liquisolid Sustained Release Tablets

The invitro drug release studies were conducted in both acidic (pH 1.2) and basic media (pH 7.5) for Eudragit RS-100 based tablets. Drug release data is shown in (Fig. 7). The drug release from all trials in acidic media was < 10% whereas in

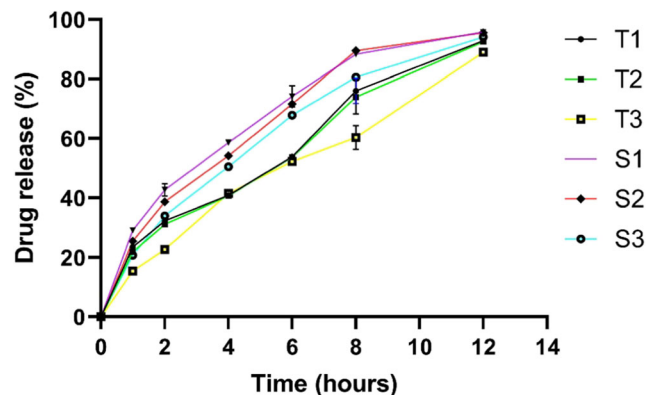


Fig. 7 In vitro drug release of formulation containing Eudragit L-100 (n = 3, ± SD) and Eudragit RS-100 (n = 3, ± SD)

Table 5 In vitro drug release kinetics of sustained release liquisolid tablets

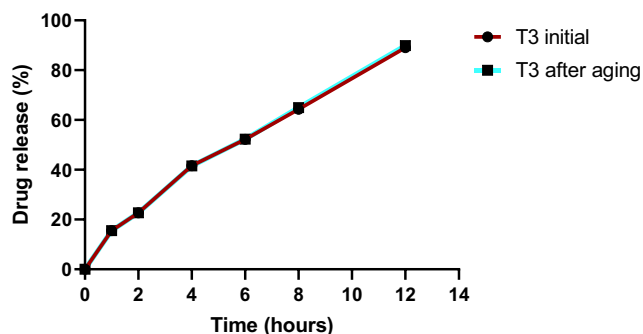
Trial #	Zero order (r^2)	First order (r^2)	Higuchi (r^2)	K–Peppas (r^2)	Hixson–Crowell (r^2)
T1	0.947	0.944	0.962	0.901	0.969
T2	0.951	0.948	0.962	0.909	0.972
T3	0.981	0.947	0.969	0.944	0.983
S1	0.871	0.991	0.989	0.932	0.983
S2	0.891	0.978	0.985	0.944	0.978
S3	0.928	0.983	0.991	0.962	0.997

basic media the drug release was $29.2 \pm 0.06\%$, $25.50 \pm 0.03\%$, $20.80 \pm 0.01\%$ after 1 h and $95.80 \pm 0.18\%$, $95.50 \pm 0.06\%$ and $94.10 \pm 0.04\%$ till the end of 12 h, respectively for trial S1, S2 and S3. It is clear from Table 5 that correlation coefficient values (r^2) of trial S1, S2, and S3, for zero-order release kinetics were less than r^2 values for first-order release kinetics (0.871, 0.891 and 0.928 < 0.991, 0.978 and 0.983), clearly indicates that the formulated sustained release tablets of Aceclofenac follow first-order release kinetics. The r^2 values of the Higuchi model for trial S1, S2 and S3 were 0.989, 0.985 and 0.990, respectively. It indicates drug release from sustained release tablets follow diffusion mechanism i.e. chemical potential gradient. Because the polymer is composed of pore network and the drug dissolved in liquid vehicle ooze out through these pores/channels. If, the polymer is hydrophilic then it will be wetted by water molecules and no retardation will occur. However, the presence of the drug in the liquid vehicle within liquisolid compacts also supports the Hixon crown model as clear from Table 5. The liquid vehicle employed in the formulation of liquisolid system impersonates an essential role in the dissolution rate enhancement or retardation [35]. Glycerin (liquid vehicle in current research work) reduces the glass transition temperature (T_g) of polymer used in the formulation due to its plasticizer effect, as a result, coalescence occurs that attributes toward lower porosity and high tortuosity within the polymer network [36]. This low porous and high tortuous fine network surrounds the drug particles and ultimately prolongs its release from the dosage form. Apart from liquid vehicle R-value (excipients ratio) was

also found a depending parameter on drug release. As the concentration of carrier material was increased the drug release was found less (Fig. 8). The consecutive reduction in drug release with increase in concentration of carrier material is shown in Table 6. It is because the high concentration of carrier polymer surrounds the drug more tightly so drug oozes out slowly. It is concluded that the Eudragit RL-100 along with glycerin provide better drug sustained release as compare with the Eudragit RS-100. This statement is justified by the fact that L-100 effectively coat the drug particles, which in turn slows down the penetration of dissolution media into the core, reduces direct contact of drug and media and thus retards the drug release. The higher dissolution 89% (Eudragit L-100 based) and 95.80% (Eudragit RS-100 based) is attributed to the presence of the drug in the molecularly dispersed state (Aceclofenac dissolved in glycerin) as compare to the micronized form of conventional dosage form [37].

Among all the trials conducted, the drug release was best sustained by formulation T3 ($88.90 \pm 0.09\%$). Also, the pre and post compression parameters for formulation T3 were also suitable as compared to other formulations (T1, T2, S1, S2 and S3), therefore formulation T3 was considered as optimized formulation.

Various kinetic release models are shown in Fig. 9. For formulation with Eudragit RL-100, the best fit linearity was found in Hixon-Crowell's plot ($r^2 = 0.983$) which indicating the release of drug from liquisolid system is by dissolution and changes in diameter or surface area of the particles following cube root law. In contrast, formulation with Eudragit RS-100 the suitable linearity was found in Higuchi's plot with $r^2 =$

**Fig. 8** In vitro drug release data after aging studies (6 months)**Table 6** Effect of carrier material concentration on drug release with standard deviation (mean \pm SD)

Trial no.	Cumulative drug release %	\pm SD
T1	92.9	0.14
T2	92.5	0.14
T3	89.0	0.09
S1	95.8	0.18
S2	95.5	0.06
S3	94.1	0.04

Fig. 9 Kinetic release models for optimized formulation. **a** Zero order. **b** First order. **c** Higuchi model. **d** Korsmeyer–Peppas model. **e** Hixson–Crowell model

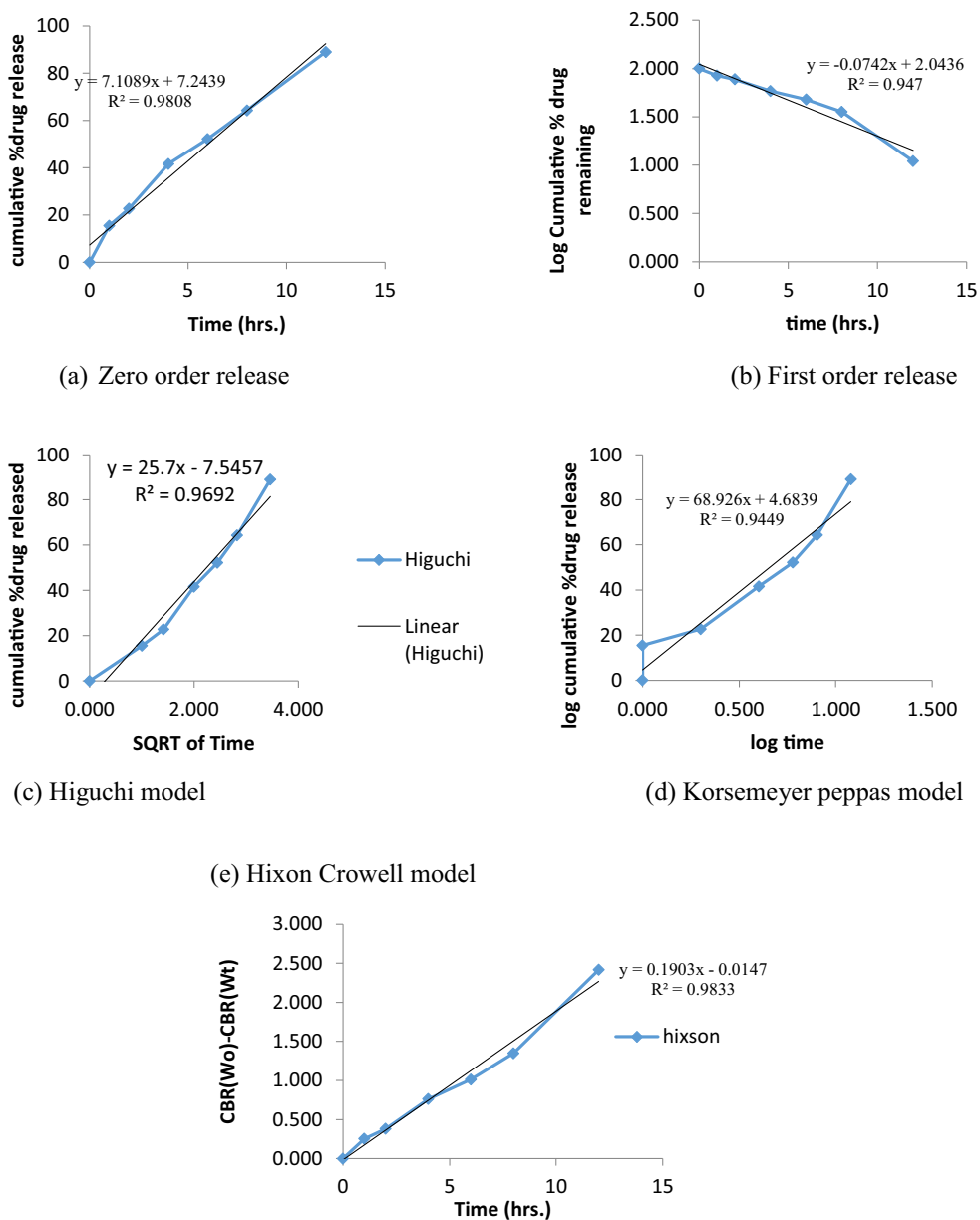
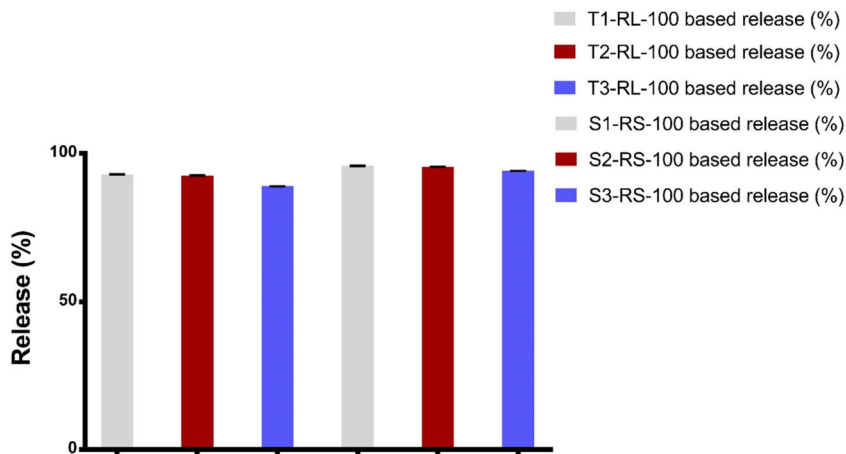


Fig. 10 Effect of carrier material concentration on drug release. Quantity of carrier material used in both Eudragit RL-100 (T1, T2, T3) and Eudragit RS-100 (S1, S2, S3) based formulation is 430 mg, 470 mg, and 500 mg, respectively



0.999. It indicates that drug release from liquisolid sustain release tablets was as a square root of time.

Quantity of carrier material used in both Eudragit RL-100 (T1, T2, T3) and Eudragit RS-100 (S1, S2, S3) based formulation is 430 mg, 470 mg and 500 mg, respectively.

Stability Studies

The storage study results data of trial T3 (optimized), for the in vitro test, is shown in (Fig. 10). After the specified time the drug release was $89.87 \pm 0.67\%$ after 12 h of the dissolution process. There was no meaningful variation between the drug release data ($89 \pm 0.09\%$) before storage. Tablets were found physically stable. Drug contents were in its official applied limit and no significant difference was found as compared to fresh tablets. It indicates that the liquisolid system is stable under unrelenting conditions of temperature and humidity.

Conclusion

It is concluded from the current research work that the liquisolid technique is an efficient tool for sustaining drug release by avoiding a swellable matrix system. The formulation was optimized in terms of excipients and Eudragit L-100 was found promising polymer for impeding drug release along with glycerin as a liquid vehicle. Drug release from formulation best fit to Higuchi and Hixon Crowell with zero-order kinetics. For comparison purposes Eudragit RS-100 based sustained release formulation was processed, nevertheless, the release was best retarded by Eudragit L-100. Solid-state characterization shows that powder was freely flowable and compressible with no drug-excipients interaction. Temperature and humidity showed no effect on the formulated dosage form ensuring that the liquisolid technique can be effectively used as a promising technique for the formulation of sustained release dosage form.

Acknowledgments I would like to acknowledge all the authors of this manuscript for their contribution.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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