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ORIGINAL ARTICLE

Dissolution Enhancement of Lycopene Compacts by Liquisolid Technique

Shaveta SHARMA, Jyoti SINGH*, Sahibpreet SINGH

Chandigarh College of Pharmacy, Chandigarh Group of Colleges, Landran, Punjab

ABSTRACT

Objectives: Lycopene is a powerful antioxidant with diverse health benefits. However, it belongs to the Biopharmaceutics Classification System II; thus, it depicts poor water solubility and dissolution. Its lipophilic nature hinders the bioavailability of this drug. To overcome these limitations, namely, poor solubility and bioavailability, several approaches have been tried so far, such as co-solvency, size reduction or micronization, complexation, adsorption on high surface area carriers, *etc.* The present research aimed to apply the liquisolid technique to prepare lycopene liquisolid compacts with an improved dissolution profile. The impact of parameters such as carrier and drug concentration percentage on drug dissolution was evaluated in liquisolid compacts.

Materials and Methods: Lycopene was extracted by Soxhlet extractionand then characterized by ultraviolet spectroscopy, infrared spectroscopy, thin-layer chromatography, and melting point. Liquisolid compacts of lycopene were formulated by using excipients such as non-volatile solvent (glycerine), carrier (Avicel PH 101, Fujicalin, Neusilin US2), disintegrant (Croscarmellose sodium), and diluent (lactose). The different formulation batches of liquisolid compacts were formulated and evaluated based on different pre-compression and post-compression parameters.

Results: Powder X-ray Diffraction (PXRD) and Fourier transform infrared spectroscopy were utilized to analyze drug-excipient interaction; these studies showed no evidence of any physical or chemical interaction between the drug(s) and the excipients. The PXRD of lycopene showed sharp and intense peaks at diffraction angles (2θ) such as 12.563, 19.176, 19.636, 20.062, 21.283, 26.629, 29.479, 30.235, and 39.997, which indicates a crystallinestructure. The PXRD of the physical mixture of lycopene and excipients showed similar sharp peaks (12.582, 19.202, 19.634, 20.045, 21.304, 26.565, 29.474, 30.250, and 40.065), indicating thatthere is no drug-excipient interaction occurring. Lycopene was extracted and characterized. IR spectroscopy and PXRD showed no drug-excipient interaction. The lycopene liquisolid compacts passed both pre-compression and post-compression evaluations within acceptable limits.

Conclusion: The formulation batch F-7, formulated with Neusilin US2 as a carrier and 40% drug concentrationshowed 98% *in vitro* drug release and thus it was selected as the optimized formulation with improved dissolution.

Keywords: Lycopene, Biopharmaceutics Classification SystemII, dissolution, liquisolid compacts, extraction, Neusilin US2

INTRODUCTION

The low solubility and dissolution of a drug are a leading hurdle for the formulation scientist. Nearly 40% of recently discovered drugs are water-insoluble.[1] Such lipophilic drugs belong to the Biopharmaceutics Classification System II (BCS II). Many approaches to enhance dissolution of water-insoluble drugs are available, such as solid dispersion, micronization, liposomes, solid lipid nanoparticles, nanosuspensions, hydrotropy, *etc*.[2-6] Poor solubility, release kinetics, dissolution rate, and photolability are prominent problems associated with most drugs. The liquisolid technique has emerged as an important approach for overcoming these challenges.[7]

This technique involves converting liquid medication (drug solubilized in a non-volatile solvent) into free-flowing, dry, and compressible powder by the addition of calculated quantities of carrier and coating material. In this technique, the drug is first solubilized in a non-volatile solvent with maximum solubility. Then, this solution is incorporated into the carrier for its absorption.[8] The adsorption of the liquid medication takes place onto the surface of the carrier particles. Next,

***Correspondence:** jsjyotisingh202@gmail.com, **ORCID-ID:** orcid.org/0000-0001-7585-4375

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coating material is added, which adsorbs liquid medication to form free-flowing, dry, and compressible powder. Afterwards, a disintegrant is added to the powder, and then it is directly compressed to form liquisolid compacts.[9] Four mechanisms are proposed for enhanced dissolution exhibited by the liquisolid compacts-increased drug surface area,[10] increased drug water solubility,[11] increased wetting ability,[12] and enhanced porosity.[13] The enhanced dissolution improves bioavailability and biological activity of the drug.[14]

Lycopene is a powerful antioxidant thatbelongs to the carotenoid family. It has 100 times greater free radical quenching properties than vitamin E. It is a redpigment, which gives colour to both fruits and vegetables. Lycopene, known for its antioxidant properties, has been found to reduce oxidative stress, a significant contributor to the development of metabolic diseases.[15] Due to its antioxidant properties, it has exhibited diverse health benefits. It has shown protective effects against many chronic diseases *in vitro* and *in vivo* studies.[16] It has demonstrated beneficial effects in cancer, diabetes, inflammatory diseases, cardiovascular diseases, skin damage, male infertility, osteoporosis, *etc*.[17]

Lycopene is completely water-insoluble in nature, leading to a major formulation problem. It has good penetration because of its lipophilic nature, hence it belongs to BCS II. Due to its low solubility, it has exhibited a poor dissolution rate.[18] This leads to low bioavailability and biological activity of the drug.[19] During the literature search, it was discovered that various nanotechnology approaches had been applied to lycopene to enhance its dissolution and improve its biological activity, such as polyethylene glycol (PEG) nanoparticles,[20] nanoliposomes,[21] inorganic nanoparticles,[22] nano-niosomes,[23] nano-structured lipid carriers,[24] Self-Microemulsifying Drug Delivery System,[25] microemulsions,[26] transfersomes,[27] ethosomes,[28] phytosomes,[29] nanocapsules,[30] carbon nanotubes,[31] polymeric nanoparticles,[32] *etc*. These nanoformulations have high production costs, stability issues, and toxicity problems, which hinder the commercialization of such formulations.[32-34]

The liquisolid technique is a recent and innovative approach for the enhancement of dissolution of lipophilic drugs, and it overcomes the drawbacks of the previously mentioned approaches. Its cheaper excipients, low cost of production, convenient manufacturing, good compressibility, and flowing property make it feasible for industrial large-scale production.[9]

The aim of this study was to prepare and evaluate lycopene-based liquisolid compacts and select the optimized formulation with improved dissolution.

MATERIALS AND METHODS

Materials

Ethyl acetate was procured from Pure Chemicals Co., Chennai. At the same time, Hexane and Acetone were obtained from Advent Chembio Pvt. Ltd., Mumbai, Monobasic potassium phosphate was purchased from Sigma-Aldrich Chemicals Pvt. Ltd., Bangalore, India, PEG 200,400 were obtained from Research-Lab Fine Chem Industries, Mumbai, India, and tween 20 and 80 were procured from Molychem, Mumbai, India, and Neusilin US2 was obtained from Ottokemi, Waliv, India.

Extraction of lycopene

Lycopene was extracted using the Soxhlet method. About 100 g of tomato was dried at 60 °C for 24 hours and thenpowdered. The dried powder was extracted using 150 mL ofethyl acetate for around 12 hours in a Soxhlet apparatus. The extract obtained was concentrated using a rotary evaporator, and then a few drops of methanol were added to precipitate out lycopene. The precipitates formed were dried and then weighed.[35]

Characterization of lycopene

IR spectroscopy

The IR spectrum of the extracted lycopene was assessed using a Bruker FTIR spectrophotometer (Alpha, Bruker, America) in the range of 4000 to 400 cm^{-1} wavelength. The IR spectral analysis was performed by mixing 5 mg of the sample with 100 mg of potassium bromide, which was subjected to a pressure of 12000 psi for about 3 min. The characteristic peaks found in the IR spectrum wereutilized to know the functional groups which are present in the spectrum. This spectrum was compared with the IR spectrum of standard lycopene for its authentication purposes.[36]

Thin-layer chromatography

Using a capillary tube, the extracted lycopene was applied to the pre-coated thin-layer chromatography (TLC) plate. This plate was kept in a developing chamber containing a mixture of hexane and acetone (70:30), which was used as the mobile phase. After the completion of the development of the TLC plate, the R_f values of the standard and extracted lycopene were contrasted. The following formula can be used to determine theR_f value:

$$R_f = \frac{\textit{Distance travelled by solute}}{\textit{Distance travelled by solvent}}$$

Melting point

The melting point determination of extracted lycopene was performed on the capillary melting point apparatus. A small amount of the sample was placed in a thin-walled capillary tube closed at one end. The capillary was then placed into the heated chamber, and the temperature was noted when the substance became completely transparent. This is considered to be the melting point.[37]

Pre-formulation studies

IR spectroscopy

The IR spectra of lycopene, Avicel PH 101, fujicalin, Neusilin US2, aerosil 200, crosscarmellose, lactose, and optimized formulation were recorded on a Bruker FTIR spectrophotometer (Alpha, Bruker) in the range of 4000 to 400 cm^{-1} wavelength to detect any drug-excipient interaction. In this analysis, IR spectral analysis was performed by mixing 5 mg of the sample with 100 mg of potassium bromide, which was pressed at 12000 psi for about 3 min.[14]

Powder X-ray diffraction (PXRD)

The PXRD pattern of lycopene, Avicel PH 101, fujicalin, neusilin US2, aerosil 200, crosscarmellose, lactose, and physical mixture was recorded on an X-ray diffractometer (Bruker Corporation, America) using Ni-filtered CuKα radiation with 1.540 Å wavelength. Data were scanned from the 10-80 ˚ 2θ range.[38]

Saturation solubility studies

To select the best non-volatile solvent, saturation solubility studies are conducted. The drug was dissolved in non-volatile solvents such as propylene glycol, glycerine, PEG 200, PEG 400, tween 20, tween 80, and distilled water. The excess quantity of the drug was dissolved in the above-mentioned non-volatile solvents. The saturated solutions formed were shaken on the water bath shaker apparatus for 48 hours at 25 ˚C at constant vibration. After the saturated solutions were kept under constant vibration, they were filtered and diluted with phosphate buffer pH 7.2. The diluted solution was analyzed by a ultraviolet-visible (UV-Vis) spectrophotometer at 363 nm. The absorbance was determined three times for each solution to calculate the solubility of lycopene.

Solubility enhancement analysis

The prepared and selected liquisolid powder was evaluated for solubility enhancement. In this, an excess quantity of liquisolid powder was dissolved in the best non-volatile solvent (glycerine). The saturated solutions formed were shaken on the water bath shaker apparatus for 48 hours at 25 ˚C at constant vibration. After saturated solutions were kept under constant vibration, it was filtered and diluted with phosphate buffer pH 7.2. The diluted solution was analyzed by a UV-Vis spectrophotometer at 363 nm. The absorbance was determined three times for each solution to evaluate solubility enhancement.[39]

Angle of slide determination

Firstly, the drug was solubilized in a non-volatile solvent in different concentrations. A binary mixture of carrier and coating material was prepared in a ratio of 20:1. Powder mixtures were formed by mixing an increasing amount of the binary mixture into the drug solution. Each powder mixture was placed on a polished metal plate, and then the metal plate was tilted till the powder started to slide. The angle (formed between the plate and the horizontal plane) at which the powder slides were noted is termedthe angle of slide. The powder mixture with a slide angle of 33 ˚ was selected for formulation preparation.[40]

Preparation of liquisolid powder

The required quantity of drug (20 mg) was weighed and dissolved with calculated quantities of non-volatile solvent (glycerine) to different drug concentration solutions (40%, 50%, and 60% *w/w*). Different carriers, i.e., Avicel PH 101 (microcrystalline cellulose), Fujicalin (dibasic calcium phosphate), and Neusilin US2 (aluminometasilicate), were selectedto select the best carrier for liqui-solid compacts. Aerosil 200 was selected as a coating material in all formulation batches. The excipient ratio was kept at a constant value of 20, as it is regarded as optimum.[41] The required quantities of the carrier and coating material were blended with the drug solution in the mortar and pestle. Crosscarmellose (5% concentration) and lactose (diluent) were mixed properly to obtain a liquisolid powder.[42] Table 1 depicts the preparation composition of all liquisolid batches.

Pre-compression evaluation of the liquisolidpowder

The pre-compression properties of the liquisolid powder are determined usingthe following parameters:

Angle of repose: This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Ten grams of powder was allowed to flow throughthe funnel from a height of 4 cm abovethe base. The height of the pile anddiameter of the base were measured, and the angle of repose was calculated using the following formula:

tan θ = h/rθ = tan-1 h/r, where = angle of repose, h = height of the heap, r = radius of the heap

Table 1. Preparation of the composition of all liquisolid batches

Group	Batchnumber	Drugconc %	W (mg)	Q (mg)	q (mg)	L_f	CCS (mg)	LSC (mg)	Lactose (mg) (Diluent)	Total weight (mg)
Group I (Avicelp H101)	F1	40	30	119.047	5.952	0.252	8.749	183.748	16.252	200
	F2	50	20	95.238	4.761	0.21	6.999	146.998	53.002	200
	F3	60	13.33	71.428	3.71	0.186	5.423	113.891	86.109	200
Group II (Fujicalin)	F4	40	30	71.428	3.571	0.42	6.249	131.248	68.752	200
	F5	50	20	57.142	2.857	0.35	4.999	104.998	95.002	200
	F6	60	13.33	47.619	2.38	0.279	4.166	87.495	112.505	200
Group III (Neusilin US2)	F7	40	30	23.809	1.19	1.26	3.749	78.748	121.252	200
	F8	50	20	19.047	0.952	1.05	2.999	62.998	137.002	200
	F9	60	13.33	14.285	0.714	0.933	2.416	50.745	149.255	200

W: Non-volatile solvent (glycerine), Q: Carrier (Avicel PH 101, Fujicalin, Neusilin US2), q:Coating material (Aerosil 200), L_f: Liquid loading factor, CCS: Crosscarmellose sodium, LSC: Liquisolid compacts weight

Bulk density: An accurately weighed quantity of powder, which was previously passed through sieve #40 United States Pharmacopeia (USP) and carefully poured into a graduated cylinder. Then, after pouring the powder into the graduated cylinder,the powder bed was made uniform without disturbing it. Then thevolume was measured directly from the graduation marks on thecylinder as mL. The volume measured was calledthe bulk volume, and the bulk density is calculated by the following formula:

bulk density = weight of powder/bulk volume

Tapped density: After measuring the bulk volume, the same measuring cylinder was setinto the tappeddensity apparatus. The tap density apparatus was set to 300 taps per minute and operated for 500 taps. Volume was noted as [V_a] and again tapped for 750 times, and volume was noted as [V_b]. If the difference between V_a and V_b is not greater than 2% then V_b is considered as the final tapped volume. The tapped density is calculated by the following formula:

tapped density = weight of powder / tapped volume

Carr's Index is one of the most important parameters to characterize the nature of powders and granules. It can be calculated from the following equation:

*Carr's Index = (tapped density - bulk density) / tapped density * 100.*

Hausner's Ratio: Hausner's ratio is an important characteristic for determining the flow property of powder and granules. This can be calculated by thefollowing formula:

Hausner's Ratio = tappeddensity / bulkdensity[43-46]

Compression

The different formulation batches of liquisolid powder were compacted into tablets by using an eight-station rotary compression machine with an 8 mm punch size, while the compression force was adjusted to get an acceptable hardness of tablets.[47]

Post-compression evaluation of the liquisolid compacts

The post-compression properties of the liquisolid compacts are determined by using the following parameters: thickness, weight variation, hardness, friability, disintegration test, and content uniformity.

In vitro release [48-53]

Mathematical modeling

The percentage cumulative quantity of the drug released from the optimized formulation batch at various time intervals was fitted into different mathematical models of drug release profile, such as Zero Order Model, Higuchi Model, First Order Model, Korsmeyer-Peppas Model, and Hixon-Crowell Model,to characterize the drug release mechanism.[54-57] The importance of *in vitro release* data in drug product development has been significant. The release kinetics can be influenced by the drug type, polymorphic form, solubility, and content proportion in the pharmaceutical dosage form. The data were fitted into various release kinetics equations, and the drug release rate was calculated. The suitability of an equation is judged forthe foremost equation using the correlation coefficient between percent drug release versus time.

RESULTS

Extraction of Lycopene

The Soxhlet extraction was conductedto extract lycopene from tomato using ethyl acetate as a solvent. The result showed that the amount of lycopene extracted from this method was 4.58±0.007 mg/g of dried matter.

Characterization of Lycopene

Infrared spectroscopy

IR spectra of standard and extracted lycopene are shown in Figures 1 and 2. The characteristic peaks of lycopene were found such as 1665.61 C=C (stretch); 1475.45 C-H (stretch); 1081.97 C-H (trans); and 717.88 C-H (out of plane). The characteristic peaks of standard lycopene were found such as 1664.46 C=C (stretch); 1476.28 C-H (stretch); 1001.69 C-H (trans); and 717.88 C-H (out of plane). While other peaks are present due to extraction solvent or minute quantities of impurity substances, the main peaks were identified as the target compounds.

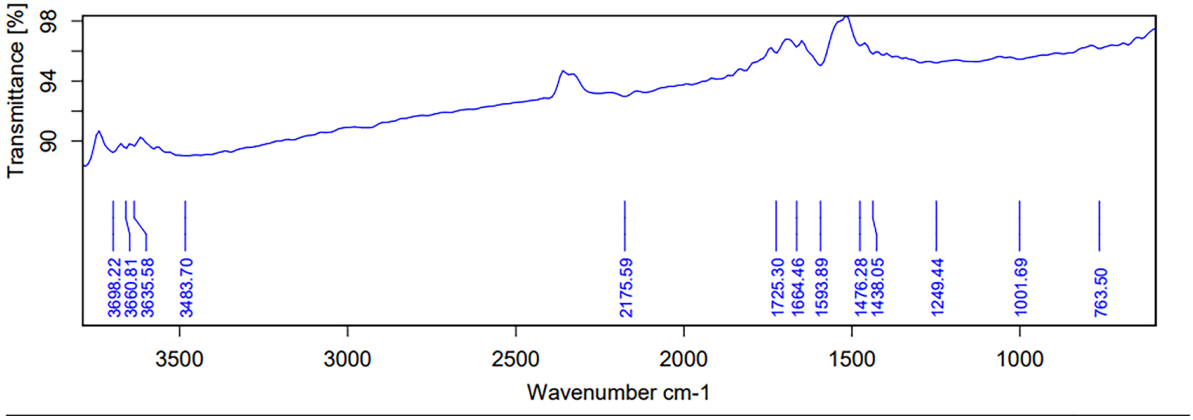

Figure 1. IR spectrum of standard

IR: Infrared

TLC

R_f value for standard lycopene and extracted lycopene was found to be the same, *i.e.*, 0.85 that is performed in pre-coated TLC plate.

Melting point

The melting point determination of extracted lycopene and standard lycopene was carried out using a capillary melting point apparatus. The melting point of extracted lycopene and standard lycopene 171-173 °C and 172 °C.

Pre-formulation studies

FTIR

Figure 3 depicts the stacked ATR of lycopene, excipients, and the optimized formulation. The IR spectrum of lycopene depicts characteristic peaks at 1664.46 cm^{-1} due to C=C (stretch), 1593 cm^{-1} due to C=C (stretch), 1476.28 cm^{-1}, and 1001.69 cm^{-1} due to C-H (trans). The IR spectrum of the physical mixture depicts similar characteristic peaks (1695.05 cm^{-1}, 1647.82 cm^{-1}, 1519.74 cm^{-1}, 1026.63 cm^{-1}), and therefore, there is no drug-excipient interaction occurring.

Saturation solubility studies

The saturation solubility studies for lycopene were conducted in different non-volatile solventssuch as glycerin, PEG 200, PEG 400, tween 20, tween 80, propylene glycol, distilled water, *etc.* Lycopene's solubility in glycerin was found to be 152.35±4.78 mg/mL.

PXRD

Figure 4 depicts the stacked PXRD of lycopene, excipients, and the physical mixture. The PXRD of lycopene showed sharp and intense peaks at diffraction angles (2θ) such as 12.563, 19.176, 19.636, 20.062, 21.283, 26.629, 29.479, 30.235, and 39.997, which indicates a crystallinestructure. The PXRD of the physical mixture of lycopene and excipients showed similar sharp peaks (12.582, 19.202, 19.634, 20.045, 21.304, 26.565, 29.474, 30.250, and 40.065), indicating thatthere is no drug-excipient interaction occurring.

Solubility enhancement analysis

The saturated solution of the liquisolid powder in glycerine was prepared. It was shaken for 48 hours, filtered, and diluted with phosphate buffer pH 7.2. The diluted solution was analyzed by UV Vis spectrophotometer at 363 nm. It was found that the optimized liquisolid powder exhibited solubility of 433.833±8.519 mg/ml in glycerine, and hence, the solubility was enhanced.

Pre-compression parameters evaluation of the liquisolid powder

Table 2 depicts the evaluation of the pre-compression parameters of all formulation batches. The angle of repose

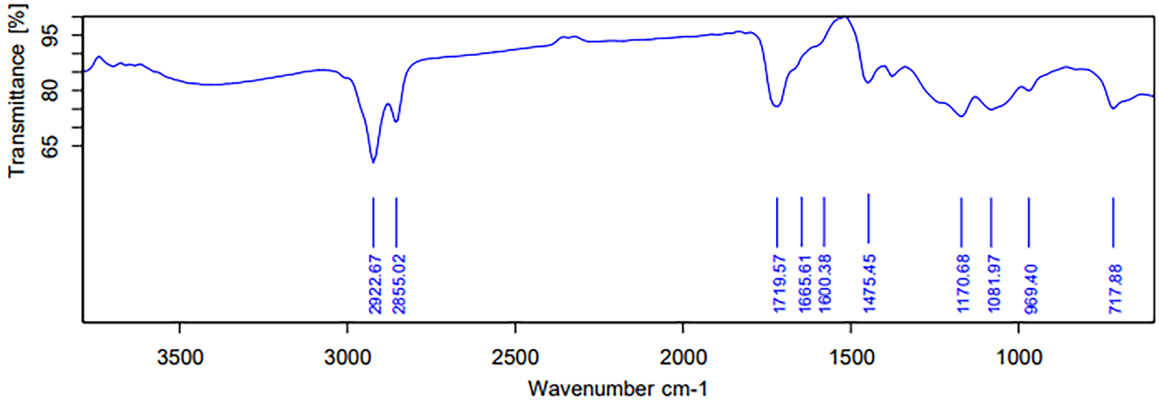

Figure 2. IR spectrum of extracted

IR: Infrared

Table 2. Pre-compression parameters evaluation of the liquisolid powder

Batch number	Angle of repose (θ)	Bulk density (g/mL)	Tapped density (g/mL)	Hausner's Ratio	Carr's Index
F-1	32.799±2.047 °	0.253±0.004	0.277±0.001	1.09±0.025	8.87±1.951
F-2	33.153±5.721 °	0.249±0.005	0.275±0.005	1.10±0.005	9.33±0.382
F-3	34.496±1.829 °	0.253±0.004	0.276±0.004	1.09±0.03	8.17±2.782
F-4	25.249±2.278 °	0.253±0.005	0.278±0.005	1.1±0.017	8.85±1.627
F-5	31.872±1.574 °	0.249±0.005	0.275±0.007	1.10±0.045	9.38±3.773
F-6	28.031±2.539 °	0.254±0.003	0.276±0.004	1.09±0.034	8.05±2.817
F-7	28.94±4.113 °	0.252±0.003	0.275±0.005	1.09±0.034	8.32±2.959
F-8	28.94±4.113 °	0.249±0.003	0.279±0.007	1.12±0.040	10.67±3.400
F-9	26.565±0.00 °	0.250±0.004	0.274±0.002	1.09±0.028	8.60±2.661

of all formulations was found to be in the range of 25.249° to 34.496 °. Bulk density and tapped density of these formulations were within the ranges of 0.249 to 0.254 g/mL and 0.274 to 0.279 g/mL, respectively. Hausner's Ratio of all liquisolid compacts batches varied from 1.09 to 1.12, while Carr's Index was within the range 8.05% to 10.67%. From theseresults, it was concluded that these formulations have excellent to good flow propertiesand thus, they can be utilized to form liquisolid compacts.

Post-compression parameters evaluation of the liquisolid compacts

The thickness of all formulation batches ranges from 3.86 to 4.10 mm. All tablets in each formulation batch showed a % deviation less than 7.5%, so they are within acceptable limits as per USP. The hardness of all formulation batches ranges from 4.166 to 6.166 kg/cm^2. It fulfills the acceptance criteria of not being less than 4 kg/cm^2. The friability of all formulation batches ranges from 0.272 to 0.582%. It was less than 1%; therefore, it fulfills the acceptance criteria as per USP. The disintegration time of all formulation batches ranges from 5.444 to 9.021 min. It was less than 30 min, which is the acceptance criterion for uncoated tablets as per USP. Hence, all formulation batches pass the disintegration test. The % drug content of all formulation batches ranges from 93.467% to 97.036% as depicted in Table 3. It was within the range of85% to 115% according to USP specifications. Hence, all formulation batches fulfill this acceptance criterion.

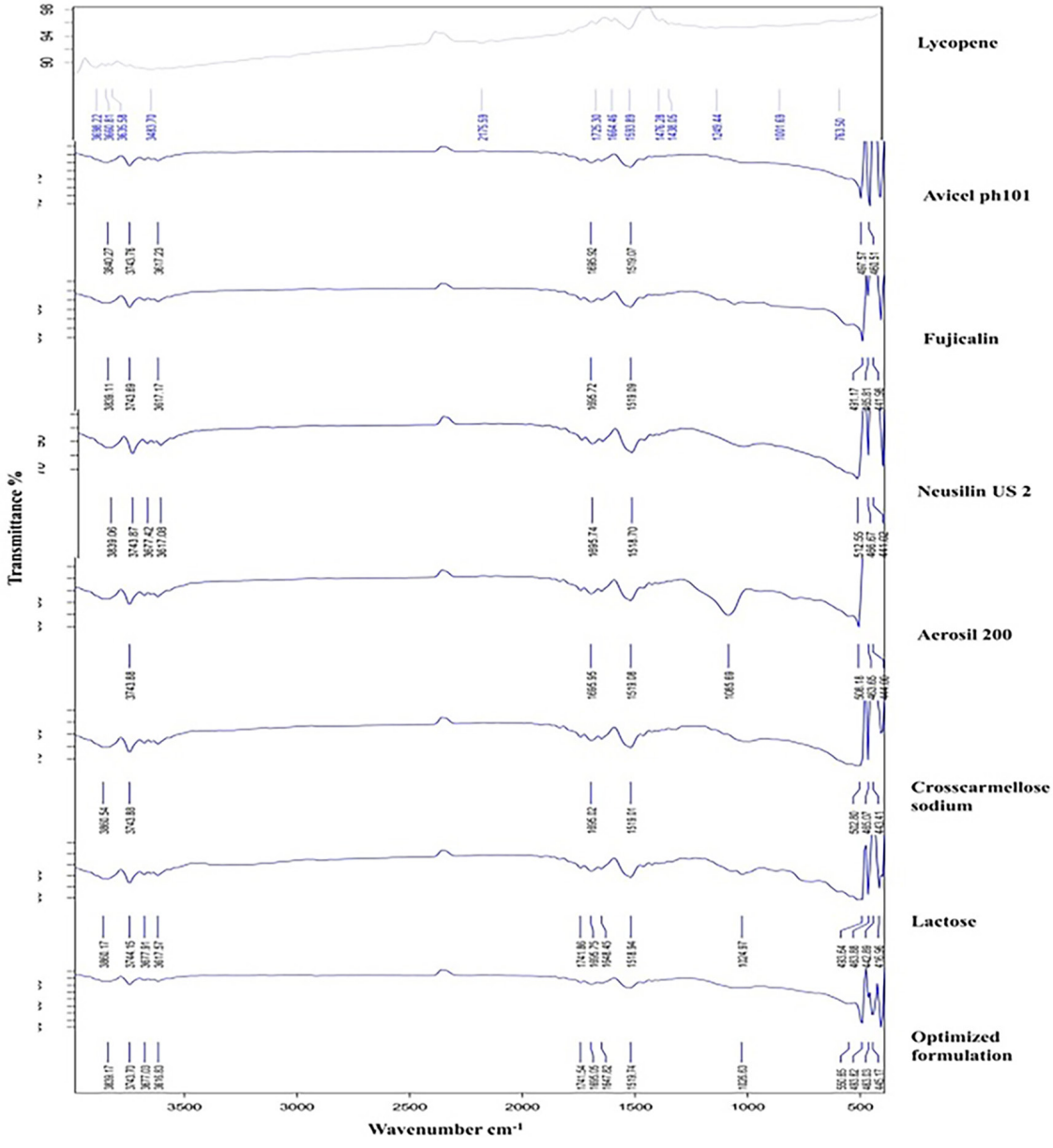

Figure 3. Stacked ATR of Lycopene, excipients and optimized formulation

ATR: Attenuated total reflectance

In vitro release

The *in vitro* drug dissolution study of all formulation batches was carried out by means of a USP type II apparatus with phosphate buffer pH 7.2. Samples for analysis were pipetted out at 5, 10, 15, 30, 45, 60, 90, and 120 min, and the absorbance was measured using a UV-Vis spectrophotometer at 363 nm. The results of an *in vitro* drug release are depicted in Table 3. The two formulation parameters, the effect of the carrier anddrug concentration, that would affect the % cumulative drug release, were investigated in this study.

Formulation batch F-1, F-2, and F-3, which were formulated with AvicelPH 101 as a carrier, with different drug concentrations (40%, 50% and 60% *w/w*), showed % cumulative drug release ranging from 67.373% to 88.873% at the 120 min time point.

Formulation batch F-4, F-5, and F-6, which were prepared with Fujicalin as a carrier with different drug concentrations (40%, 50%, and 60% *w/w*), showed % cumulative drug release ranging from 76.85% to 94.61% at a 120 minute time interval.

Formulation batch F-7, F-8, and F-9, which were prepared with Neusilin US2 as a carrier, with different drug concentrations (40 %, 50 %, and 60 % *w/w*), showed a cumulative drug release percentage ranging from 79.617% to 98.033% within a 120-minute time interval. Figure 5 depicts the *in vitro* drug dissolution profile of formulation batches F-7, F-8, and F-9.

Formulation batch F-7 is considered to be an optimized formulation with a maximumcumulative drug release of 98.033% after 120 minutes.

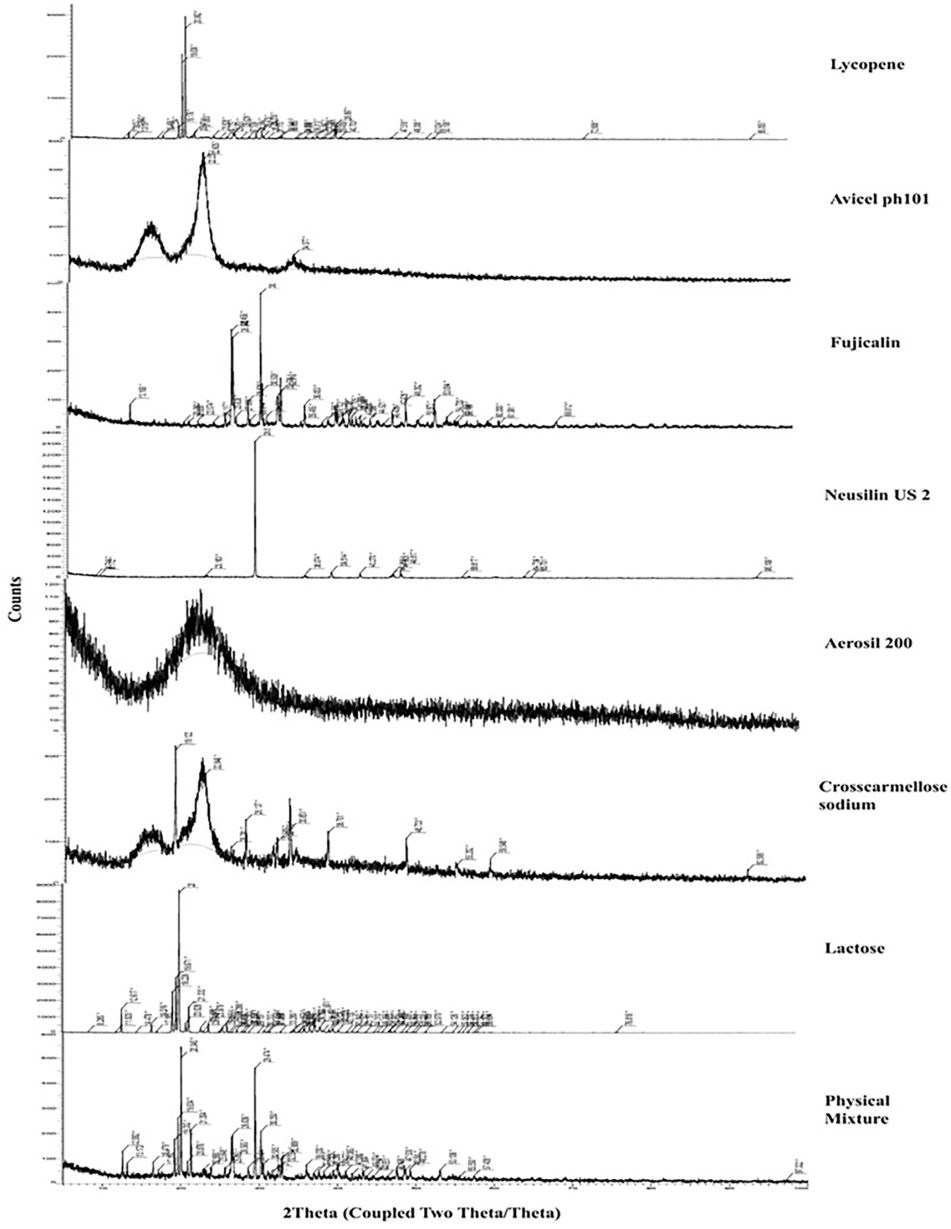

Figure 4. Stacked PXRD of lycopene, excipients, and physical mixture
PXRD: Powder X-ray Diffraction

It was observed that formulation batches prepared with Neusilin US2 as a carrier have higher drug release than those prepared with Fucigeland Avicel PH 101.

The reason behind this phenomenon is that Neusilin US2 (300 m^2/g) has a higher specific surface area than fujicalin (40 m^2/g) and Avicel PH 101 (1.18 m^2/g). A high specific surface area indicates high porosity. The carrier with high porosity enhances the penetration of the dissolution medium, thereby leading to improved dissolution.

It was also observed that the formulation batches with 40% drug concentration showed a higher drug release than formulation batches with 50% and 60% drug concentration.

It has occurred because formulation batches with 40% drug concentration have a higher amount of non-volatile solvent than formulation batches with 50% and 60% drug concentration. The increase in the amount of non-volatile solvent causes improved dissolution due to an increase in drug surface area, enhanced aqueous solubility, and better wetting properties of the drug.

Mathematical modeling

The *in vitro* drug dissolution profile of the F-7 formulation batch was fit to models such as the Zero Order model, Higuchi model, First Order model, Krosmeyer-Peppas model, Hixson-Crowell model, *etc*., to characterize the drug release mechanism. Figure 6 depicts the Higuchi model for F-7. The value of the regression coefficient (R^2) was determined in each model to choose the best-fit model. It was found that the Higuchi model for F-7 has the highest R^2 value of 0.989, and it was selected as the best fit model.

The Higuchi model is used to describe the dissolution profile of the matrix system in which drug diffusion takes place. The dissolution medium enters the formulation, and the drug is released from it by the diffusion process. Thus, optimized formulation F-7 follows a diffusion-typedrug release. In this model, the fraction of drug released is dependent on the square root of time. Such a model is usually followed by matrix systems. It is depicted by the following equation:

$$Q = K_H\sqrt{t}$$

Where,

Q = cumulative amount of drug release at *time t*

K_H = Higuchi dissolution constant

Table 3. Post-compression parameters evaluation of the liquisolid compacts

Batch number	Thickness (mm)	Weight variation (mg)	Hardness (kg/cm²)	Friability, %	Disintegration time (min)	Drug content, %	Cumulative drug release (120 min) %
F-1	4.00±0.105	200.105±2.452	4.166±0.288	0.439±0.276	6.409±0.17	97.036±2.259	88.873±0.095
F-2	3.98±0.138	201.32±4.214	4.5±0.5	0.526±0.034	6.433±0.138	93.467±2.806	75.873±0.989
F-3	4.09±0.190	199.72±4.389	5.5±0.5	0.582±0.157	5.444±0.106	94.982±0.556	67.373±0.667
F-4	3.93±0.075	200.855±3.037	4.33±0.288	0.373±0.301	7.656±0.071	95.487±3.097	94.610±0.144
F-5	4.10±0.057	200.585±2.529	6.166±0.288	0.585±0.089	9.021±0.395	95.218±1.741	86.060±0.629
F-6	4.10±0.057	200.28±2.04	4.666±0.288	0.272±0.333	6.781±0.248	96.127±2.176	76.850±1.439
F-7	3.86±0.075	200.79±2.272	5.166±0.288	0.354±0.166	8.351±0.188	95.252±2.042	98.033±0.748
F-8	3.99±0.080	200.91±2.058	5±0.5	0.493±0.258	6.491±0.33	95.925±2.312	88.983±1.396
F-9	4.07±0.229	200.095±1.907	4.666±0.763	0.44±0.314	6.613±0.152	95.555±1.924	79.167±0.677

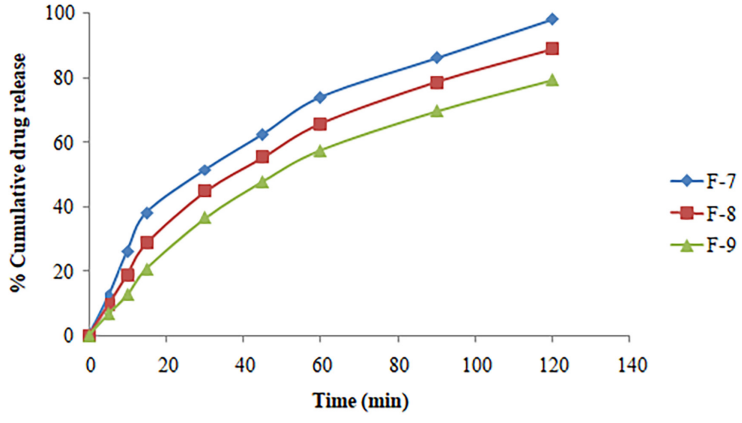

Figure 5. Graphical representation of the *in vitro* drug dissolution profile of formulation batches F-7, F-8, and F-9

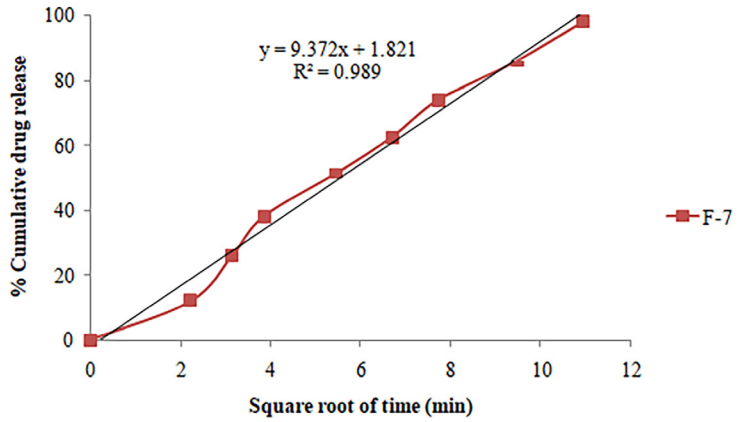

Figure 6. Higuchi model for F-7

DISCUSSION

The IR spectral characteristic peaks were observed for the physical mixtures and the results showed that lycopene showed no evidence of physical or chemical interaction. All FTIR spectra suggest that the drug and excipients had no interaction. In glycerin, lycopene has shown the maximum solubility of 152.35 mg/mL, this would facilitate the dissolution rate by improving the surface area as it will be molecularly dispersed.

Neusilin (Magnesium Alumino-metasilicate) has a high SSA and liquid absorption capacity, which aids in the assimilation of a greater amount of liquid material into the liquisolid structure. *In vitro* drug release study demonstrates that lower drug proportion in glycerin results in higher drug release, on the other side, the Higuchi model indicates that drug release is dissolution rate controlled, as evidently shown in themathematical modelling.

CONCLUSION

This research aimed at developing lycopene-based liquisolid compacts with improved dissolution. Different formulation batches of lycopene-based liquisolid compacts were formulated using varying carrier and drug concentration percentages. The results indicated that IR spectroscopy and PXRD showed no drug-excipient interaction. Moreover, all formulation batches passed pre-compression and post-compression evaluation. F-7 formulation batch with Neusilin as carrier and 40% drug concentration having 98% *in vitro* release was found to be the optimized formulation with maximum dissolution. Thus, this research concludes that Neusilin isthe most effective carriercompared toFujicalin and Avicel. Thus, this technique that uses Neusilin as a carrier can toenhance the dissolution of lycopene.

Ethics

Ethics Committee Approval: Not required.

Informed Consent: Not required.

Footnotes

Authorship Contributions

Concept: J.S., Design: J.S., Data Collection or Processing: S.S., Analysis or Interpretation: S.S., J.S., Literature Search: S.S., Writing: S.S.

Conflict of Interest: The authors declare no conflicts of interest.

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