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Original article

Solubility enhancement of some poorly soluble drugs by solid dispersion using Ziziphus spina-christi gum polymer

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ABSTRACT

A high percentage of marketed drugs suffer from poor water solubility and require an appropriate technique to increase their solubility. This study aims to compare physically modified and unmodified gum polymers extracted from *Ziziphus spina-christi* fruits as solid dispersion carriers for some drugs. Taguchi Orthogonal Design (L9) was chosen for the screening and optimization of the solid dispersions. The design has four factors: type of drug, type of polymer, type of solid dispersion process, and drug to polymer ratio. Each factor was varied in three stages and the total number of runs was 9 in triplicate. The polymer was physically modified by heating (M1ZG) or freeze-drying (M2ZG). The drugs were selected according to the biopharmaceutical classification system, namely loratadine and glimepiride (class II) and furosemide (class IV). Drugs were dispersed in the polymer in three different ratios 1: 1, 1: 2, and 1: 3. Solid dispersions were made by co-grinding, solvent evaporation, and kneading methods. Modified and unmodified polymers were characterized in terms of their organoleptic properties, solubility, powder flowability, density, viscosity, swelling index, and water retention capacity. Solid dispersions were characterized in terms of percentage practical yield, solubility improvement, and drug compatibility. The results showed that the organoleptic properties of polymers were not changed by the gum modification. The swelling index of the polymer was doubled in M1ZG. The viscosity and water retention capacity of the polymer was increased in both modified polymers. All solid dispersions showed a high practical percentage yield of more than 93%, the higher values being more associated with loratadine and furosemide than with glimepiride. The improvement in solubility was observed in all solid dispersions prepared, the values varying with the pH of the medium and the method of modification. The FTIR results indicated that there was no chemical interaction between these drugs and the polymer used. Analysis of the results according to the Taguchi orthogonal design indicated 51 folds aqueous solubility enhancement for loratadine using M2ZG polymer at a ratio of 1: 3 of Drug: polymer. This study showed the possibility of improving the solubility of other poorly soluble drugs.

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1. Introduction

1.1. Natural excipients

An excipient is defined as a substance that is used as a medium for the administration of a drug. Applications of natural polysaccharide polymers in pharmaceutical formulations include assisting with drug delivery system processing, protecting, assisting, or improving drug stability and bioavailability or patient acceptance, assisting with product identification, or enhancing other properties of the overall safety, efficacy, or delivery of the drug during storage or use (Prajapati et al., 2013). Several pharmaceutical excipients of plants origin are commonly used in the pharmaceutical industry. Since vegetable sources are renewable and can be cultivated and harvested sustainably, a constant supply and availability of raw materials are guaranteed. However, substances of plants origin also harbor some potential challenges, such as biosynthesis in small quantities, and are structurally complex mixtures that can differ depending on the location of the plants and other variables such as seasonal variation. Challenges include also slow and expensive isolation and cleaning process (Singh et al., 2016).

Ziziphus spina-christi is a scientific name of a plant, the common name of which in Yemen, Saudi Arabia, Sudan, and some Arab countries are Sidr, Nebeq, or Nabag. The genus *Ziziphus* belongs to the *Rhamnaceae* family. The plant is mentioned many times in the Holy Quran and is very widely used in Arab countries. All parts of this plant are used by the native Arabs to maintain a healthy lifestyle. *Ziziphus spina-christi* is used in folk medicine as a soothing, detoxifying, anodyne, emollient, and stomach remedy, for toothache, astringent, and as a mouthwash (Saied et al., 2008).

Most of the approved drugs and new chemical substances developed in the pharmaceutical industry are practically insoluble in water. The solubility and dissolution properties of drugs play an important role in the process of formulation development, so solubility is a major challenge for formulation scientists (Savjani, Gajjar and Savjani, 2012; Tiwle et al., 2012). To exert better therapeutic efficacy or better bioavailability, the drug must have a high rate of dissolution and high aqueous solubility. Many polymers have limitations in improving the solubility of poorly water-soluble drugs because of their high viscosity. The use of low viscosity, high swellable polymers offers a better alternative for these types of polymers. The use of natural polymers is more advantageous because of their low cost, biocompatibility, and biodegradability. Most of these polymers are hydrophilic and swell after water absorption and form a viscous gel layer around the dosage form, which leads to delayed/delayed drug release (Patel et al., 2008). The properties of the carrier have a major influence on the dissolution properties of the dispersed drug. A carrier should meet the following criteria to increase the rate of dissolution of a drug: water-soluble for rapid release or insoluble for delayed-release, physiologically inert, the melting point should not exceed 200 °C, thermal stability up to the melting point, non-toxic, non-irritating, and chemically compatible (Kumar and Kumar, 2017).

1.2. Solid dispersion

Solid dispersions (SDs) are defined as the dispersion of one or more active ingredients in an inert carrier or matrix in the solid-state. SDs are viewed as single-phase mixtures of an active ingredient and water-soluble polymers that are believed to provide improved aqueous dissolution and oral bioavailability (Newman et al., 2012). The polymer has two main functions; on the one hand, it contributes to the long-term storage stability of the drug by inhibiting crystallization in the solid-state, and on the other hand, it helps to maintain a desired degree of supersaturation in the dissolution by preventing solvent-mediated crystallization. The SDs can be used to improve the bioavailability of poorly water-soluble drugs with different physicochemical properties since they allow the gastrointestinal (GI) concentrations to be increased by increasing their apparent solubility and rate of dissolution (Prasad, Jain and Garad, 2017). Particle size reduction, agglomeration, wetting, separation of the individual particles of the drug by the polymer particles, and the subsequent prevention of drug precipitation on contact with an aqueous medium are some of the factors that help improve bioavailability (Tran et al., 2019).

In the development process of SDs, the selection of the polymer is fundamental as it affects the bioavailability, manufacture, and stability of the final formulation. A carrier must have other desirable properties such as being pharmacologically inert and non-toxic and chemically compatible with the drug, in addition to solubility in multiple solvents if the solvent method is used for SD preparation, or thermostable with a low melting point if the fusion method is chosen (Tekade and Yadav, 2020).

According to their molecular arrangement, SDs can be divided into four classes: eutectic mixtures, mixed crystals, amorphous mixed crystals as well glass solutions, and glass dispersions. Various methods are used to prepare a solid dispersion system. The processes used to make SDs are based on solvent evaporation and melt extrusion technologies. These processes include melt/melt processes, solvent processes, melt solvent processes (melt evaporation), melt extrusion processes, lyophilization techniques, melt agglomeration processes, the use of surfactants, electrospinning and supercritical fluid (SCF) technology. The main disadvantage of SDs is their physical instability, as the drug tends to recrystallize due to both thermodynamic and kinetic driving forces (Vasconcelos et al., 2007).

1.3. Modification of natural carriers for the solid dispersion

There are several natural carriers for the production of solid dispersions, however, due to their properties, limitations, and undesirable properties, they need to be modified. In general, when heated to different temperatures, natural carriers lead to changes in their properties such as viscosity, water holding capacity, bulk and tap density, swelling index, Carr's index, flow properties, etc. Such changes in properties can meet the desired criteria required by an ideal carrier for the production of solid dispersion. Natural carriers, especially gums, when overheated and, due to charring, the active properties could be lost. Possible changes in the color of modified natural carriers must be identified. Other modifications include the use of UV light and freeze-drying (Babu et al., 2002; Shejul, Deshmane and Biyani, 2014).

This study aims at investigating the enhancement of the aqueous solubility of some poorly soluble drugs using solid dispersion techniques based on modified and unmodified *Ziziphus spina-christi* gums. Modification of the gum polymer was physically carried out by heating and freezing drying.

2. Materials and methods

2.1. Materials

Ziziphus spina-christi fruits as dried fruits were brought from the local market; The pure drug loratadine was generously donated by the Blue Nile pharmaceutical factory, Sudan; Glimipride from Azal Pharma, Sudan; Furosemide from Abdelmoniem Medical Industries CIMA, Sudan; Potassium dihydrogen orthophosphate anhydrous was purchased from (Central Drug Houser (P) Ltd., India); Dipotas-

sium hydrogen orthophosphate and ethanol from (S. D. Fine-CHEM Limited (SDFCL), Mumbai); Hydrochloric acid from (Atom Scientific, UK).

2.2. Methods

2.2.1. Extraction of Ziziphus gum polymer

Ziziphus spina-christi fruits were washed with water to remove dirt and crushed. The crushed fruit material was soaked in an excess of distilled water for 72 h in a refrigerator. The fruit bulb was then manually separated and squeezed in a muslin bag to remove the mark from the filtrate and allowed to stand for 24 h in a refrigerator. The supernatant was then taken by decantation as a clear mucilaginous solution, equal volume of ethyl alcohol was added to the filtrate to precipitate the mucilage, the mucilage was separated, dried in an oven at about 45 °C, powdered and passed through sieve No. 80 as a faint brown fine powder. The obtained powder was kept in a dry amber screw-capped glass container until further use (Pant, Malviya and Sharma, 2015).

2.2.2. Modification of Ziziphus gum polymer (ZG)

Two methods were used. The first method is by heating the gum polymer at 120 °C in a hot air oven for 2 h (M1ZG) (Babu, Prasad and Murthy, 2002). The second method, in which gum polymer freeze-drying for 24 h (M2ZG).

2.2.3. Characterization of ZG polymers

2.2.3.1. Macroscopic properties. The polymers were examined for their color, taste, and odor.

2.2.3.2. Solubility. The solubility of the gum and their modification were determined in distilled water, methanol, ethanol, and DCM. One gram of the gum sample was added to 50 ml each of the above-mentioned solvents and left overnight. 25 ml of the clear supernatants were taken in small pre-weighted evaporating dishes and heated to dryness over a digital thermostatic water bath. The weights of the residue concerning the volume of the solutions were determined using a digital top loading balance and expressed as the percentage solubility of the gums in the solvents (Ibrahim, Abdulkadir and Muhammed, 2017).

2.2.3.3. Swelling index. The quantity of 1 g of each ZG polymer was weighed exactly and transferred to a 100 ml measuring cylinder. The initial volume of the powder was noted. The gum was then thoroughly dispersed in 100 ml of distilled water by vigorous shaking. The measuring cylinder was kept at ambient temperature and humidity for 24 h. The volume occupied by ZG polymer sediment after 24 h was noted. The swelling index, expressed in percent, was calculated according to the following equation:

$$SI = (X_1 - X_0/X_0)x100$$

where:

X_0 is the initial height of the powder in the measuring cylinder, X_1 is the height of the swollen gum after 24 h (Patel et al., 2008; Rodde et al., 2014).

2.2.3.4. Water retention capacity. After the swelling index study had been carried out, the contents of the measuring cylinder were filtered with a muslin cloth, and the water was allowed to drain completely into a dry 100 ml measuring cylinder and the volume of the water collected was noted. The water retained by the sample was determined as the difference between the original volume of slime and the volume of water drained off. The amount of water retained per unit volume of a polysaccharide is referred to as the water retention capacity or water absorption capacity (Tekade and Gattani, 2009).

2.2.3.5. Viscosity Measurement:. The viscosity of a 1% aqueous solution of each UMZG, M1ZG, and M2ZG polymers was measured according to USP specifications using a (BROOKFIELD LV DV II + Pro Viscometer, BROOKFIELD Engineering Laboratories, USA) using a spindle 61. measured at 200 rpm (Rodde et al., 2014).

2.2.3.6. Angle of repose. The angle of repose was measured by the fixed funnel method. An accurately weighed 10 g of each UMZG, M1ZG, and M2ZG polymer was poured through a funnel. The height of the funnel was adjusted so that its tip just touched the top of the pile of powder below. The powder was allowed to flow freely through the funnel onto the pile of powder and the angle of repose was calculated using the following equation:

$$Tan\theta = h/r$$

Where: h is the height of the powder pile and r is the radius of the powder pile (Rodde et al., 2014).

2.2.3.7. Compressibility index and Hausner ratio. The loose bulk density (LBD) and the tapped bulk density (TBD) of each ZG polymer powder were determined. A 10 g quantity of powdered gum was poured into a 100 ml calibrated graduated cylinder and the initial volume was recorded. The cylinder was then dropped onto a hard surface using (Digital Automatic Tap Density Test Apparatus VEEGO VTAP / MATIC II, (Veego Instrument Corporation, India). Tapping was continued until no further change in volume was detected (Rodde et al., 2014). The LBD and TBD were calculated using the following equation:

$$LBD = weight\ of\ the\ powder/initial\ volume\ of\ the\ pack$$

$$TBD = weight\ of\ the\ powder/tapping\ volume\ of\ the\ pack$$

The compressibility index (Carr's index) was determined using the following equation:

$$Carr's\ index(\%) = (TBD - LBD/TBD)x100$$

The Hausner ratio was determined using the following equation:

$$Hausner\ ratio = TBD/LBD$$

2.2.3.8. pH value. The pH of 1% w/v aqueous solution of each ZG polymer was determined with a pH meter (JANEWAY, 3510 pH Meter, Bibby Scientific Ltd, United Kingdom) (Rodde et al., 2014).

2.2.4. Preformulation studies

2.2.4.1. Validation method for the assay.

2.2.4.1.1. Scanning for λ_{max} of the drugs. The drug Glimipride (GLM), Loratadine (LOR), and Furosemide (FUR) solutions were scanned to obtain the spectrum and λmax in the range of 200–400 nm using (UV JANEWAY, 7315 Spectrophotometer, Bibby Scientific Ltd, United Kingdom).

2.2.4.1.2. Standard calibration curve of the drugs tested. 100 mg GLM, LOR, or FUR were transferred to a 100 ml volumetric flask and dissolved with methanol. 10 ml of the sample was taken from each solution and diluted to 100 ml with distilled water to form 100 µg / ml (stock solution). Then volumes of 0.4, 0.6, 0.8, 1 and 1.2 ml were withdrawn from the stock solution and diluted to 10 ml to give a solution with a concentration of 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg /ml and 12 µg/ml for GLM and 0.3, 0.4, 0.5, 0.6 and 0.7 ml from the stock solution diluted to 10 ml to make solutions with concentrations of 3 µg/ml, 4 µg/ml, 5 µg/ml, 6 µg/ml and 7 µg/ml for LOR and FUR. The absorbance was measured at λ_{max} for each drug using (UV JANEWAY, 7315 Spectrophotometer, Bibby Scientific Ltd, United Kingdom) and the graph was plot-

ted for absorbance versus concentration (Bosch et al., 2008; Karthik et al., 2008).

2.2.4.1.3. Linearity. Fresh aliquots were prepared from the stock solution at different concentrations. The absorbance of samples was measured against the blank using (UV JANEWAY, 7315 Spectrophotometer, Bibby Scientific Ltd, United Kingdom).

2.2.4.1.4. Precision. The precision (intra-day precision) of the method was assessed by measuring the three independent test samples. The inter-day precision of the method was also assessed with two different analysts and different days in the same laboratory. The relative standard deviation (% RSD) was obtained (Betz, Brown and Roman, 2011).

2.2.4.1.5. Accuracy. The accuracy of the method was confirmed by examining the recovery at 3 different concentrations by replicate analysis (n = 3) and the percent drug content was measured.

2.2.4.1.6. Sensitivity. The detection limit of an individual analytical method is the lowest amount of analyte in a sample that can be detected but not necessarily quantified as an exact value. The limit of quantification of a single analyte in a sample that can be quantified with suitable precision and accuracy was the LOD and the LOQ and can be determined using the formula:

$$LOD = 3.3(SD/S)$$

$$LOQ = 10(SD/S)$$

Where S is the average value of the slope of the calibration curves and SD is calculated using the values of the y-axis intercepts of the regression equation (Betz, Brown and Roman, 2011).

2.2.4.2. Preparation of solid ZG dispersions.

2.2.4.2.1. Preparation method of solid dispersions. For the kneading process, the required amounts of each drug and each ZG polymer were kneaded in a mortar using ethanol. The mixture was dried to constant weight in a hot air oven. The dried weight was sieved through sieve No. 80. The mixture was stored in the airtight container at room temperature.

For the solvent evaporation process, the required amounts of each drug and each ZG polymer, in a 1: 2 ratio of ethanol: water were dissolved by continuously stirring with a magnetic stirrer for one hour at room temperature. Ethanol was removed under reduced pressure using a rotary evaporator kept at 40 °C until all solvents were evaporated. The solid dispersions formed were further dried in an oven at 40 °C for 12 h and then passed through sieve No. 60. All of the resulting solid dispersions were scraped off, pulverized in a mortar, and sieved through sieve No. 60. All solid dispersions were then stored in amber glass vials and kept in a desiccator at 20 ± 1 °C. until further analysis (Biswal et al., 2008; Jahan et al., 2011; Kumar, Rani and Kumar, 2011).

For the co-grinding process, the required amounts of each drug and ZG polymer were placed in the mortar and properly triturated together. The mixture was then sieved through sieve No. 80. The mixture was stored in the airtight container at room temperature (Hardatt et al., 2016).

2.2.4.2.2. Taguchi orthogonal array (TOA). L9 (34) TOA was used in this study to define the optimal conditions related to the selected factors to produce solid ZG dispersions for GLM, LOR, and FUR with high entrapment efficiency and minimum particle size and required potential. The design included four factors on three levels as shown in Table 1. These factors were the type of drug, the method of modifying the ZG polymer, the method of solid dispersion preparation, and the drug to polymer ratio. Table 2 shows formulations of solid ZG dispersions designed by L9 Taguchi Orthogonal Array (TOA) Design. As shown in Table 2; the array L9 (34) had 9 rows and four columns on three levels. Each of the nine experiments was carried out in triplicate, making a total of 27 experiments as one block, and it was carried out in two blocks.

Table 1
Factors and levels in L_9 (3^4) Taguchi orthogonal array (TOA) design.

Factors		Levels		
		1	2	3
A	Type of drug	GLM	LOR	FUR
B	Type of polymer	UMZG	M1ZG	M2ZG
C	Method of solid dispersion	KN	SE	CG
D	Ratio Drug: polymer	1:1	1:2	1:3

Unmodified Ziziphus Gum (UMZG), Modified Ziziphus Gum by heating (M1ZG), and Modified Ziziphus Gum by freeze-drying M2ZG. Co-grinding (CG), Solvent Evaporation (SE), and Kneading (KN) methods for the preparation of solid dispersion.

Table 2
Formulations of ZG SDs designed by L_9 (TOA) design.

SD. code	A	B	C	D
SD1	1	1	1	1
SD2	1	2	2	2
SD3	1	3	3	3
SD4	2	1	2	3
SD5	2	2	3	1
SD6	2	3	1	2
SD7	3	1	3	2
SD8	3	2	1	3
SD9	3	3	2	1

SD: Solid dispersion; A: Type of drug; B: Type of polymer; C: Method of solid dispersion; D: Ratio Drug: Polymer.

The solid dispersions produced were characterized by the percentage practical yield, the solubility improvement, and the drug compatibility. The results were also confirmed by calculating the percentage contribution (PC%) of each factor involved in our formula using the following equation:

$$PC\% = \frac{SS'}{SStotal} X\,100$$

Where: ss' is the purified sum of squares and SS_{total} is the total sum of squares.

2.2.4.3. Characterization of the prepared ZG solid dispersions.

2.2.4.3.1. Determination of solubility in various media. Solubility of solid dispersions and pure drugs GLM, LOR, and FUR in distilled water, 0.1 N HCl (pH 1.2), pH 6.8, and pH 7.4 Phosphate buffer was carried out. An excess drug (100 mg) or equivalent weight of SDs were dissolved in 20 ml of each medium in an Erlenmeyer flask and kept on a mechanical shaker using a shaking water bath for 24 h, followed by filtration of the dispersions. The dispersions were then centrifuged for 10 min, the supernatant was filtered off, suitably diluted and the absorbance was recorded. All experiments were performed in triplicate (Jahangiri et al., 2015; Dong et al., 2018).

2.2.4.3.2. Percent practical yield. Percent Practical Yield has been calculated to know the percentage yield or efficiency of a method and thus aids in selecting the appropriate production method. The collected SDs were weighed and compared with the initial weight (Yi et al., 2014). The percentage yield of SDs was determined using the following formula:

$$\text{Percentage yield} = \frac{\text{weight of prepared solid dispersion}}{\text{weight of drug} + \text{carrier}} X\,100$$

2.2.4.3.3. Compatibility studies with pharmaceutical excipients. Potassium bromide was mixed with 10 mg of the sample. The mixture was properly triturated with mortar and pestle. The mixture was compressed into a disk using a hydraulic press. The sampling

frequency range was kept in 4000–400 cm-1. Infrared absorption spectra of GLM, LOR, FUR, UMZG polymer, M1ZG polymer, M2ZG polymer, and the prepared LOR-ZG solid dispersions were obtained using an FTIR spectrophotometer (IRTracer-100 FTIR SHIMADZU, Japan) (Maurya, Belgamwar and Tekade, 2010; Hardatt et al., 2016).

3. Results and discussion

3.1. Characterization of ZG polymer

Unmodified and modified forms of gum were evaluated about various physicochemical properties and the results are shown in Table 3. ZG showed no change in organoleptic properties and pH after modification by heat or freeze-drying, which indicates its stability. The powder flowability and compressibility of ZG were reduced more by freeze-drying than by heat modification. This can be attributed to the different properties of the powder bed obtained. It has been found that the viscosity of ZG is increased depending on the type of modification process. The heating method increased the viscosity of ZG by 33%, while the freeze-drying method only increased it by 10%. It was known that temperature changes the viscosity of natural gums by allowing more hydrophobic bonds such as hydrogen bonds and by improving the crosslinking of the polymer. ZG showed higher cross-linking from heat than from freeze-drying. This result suggests the use of thermal modification to improve the performance of the ZG polymer. In terms of water retention, the modification of ZG improved the capacity and the freeze-drying modification showed the highest values. It should be noted that the water retention capacity of gums depends on the functional groups in the gums that can bind water molecules. Therefore, the water absorption capacity depends on the number and type of water-binding sites. The results of this study suggest that freeze-drying can increase the porosity of ZG and its water-binding sites. ZG showed a different swelling behavior with different modification methods. The heat modification of ZG showed an improvement in the swelling index of about 84%, while the freeze-drying showed no significant effect compared to UMZG. The swelling index (%) represents the increase in the volume of the polymer network.

3.2. Method validation for drugs assay

3.2.1. λ_{max} scanning and linearity of calibration curves

After scanning, λmax was found to be 240 nm, 225 nm, and 245 nm for GLM, LOR, and FUR respectively. A linear relationship between concentrations and absorbances was indicated for all cal-

Table 3
Physicochemical characterization of Ziziphus gum polymers and their modified forms.

Parameters		UMZG	M1ZG	M2ZG
Macroscopic property	**Color**	Pale brown	Pale brown	Pale brown
	Taste	Sweet	Sweet	Sweet
	Odor	Odorless	Odorless	Odorless
Solubility	**Water**	Practically insoluble	Practically insoluble	Practically insoluble
	Methanol	Practically insoluble	Practically insoluble	Practically insoluble
	Ethanol	Practically insoluble	Practically insoluble	Practically insoluble
	DCM	Practically insoluble	Practically insoluble	Practically insoluble
Swelling index (% ± SD)		966.6 ± 33.3	1783.3 ± 76.37	891.6 ± 14.43
Water retention capacity (ml ± SD)		18.667 ± 1.154	20.667 ± 0.577	22 ± 1
Viscosity (cps ± SD)		15.667 ± 0.208	20.7 ± 0.435	17.167 ± 0.152
Angle of repose (° ± SD)		39.82 ± 0.531	40.66 ± 0.097	41.72 ± 0.058
pH value (±SD)		4.24 ± 0.034	4.25 ± 0	4.26 ± 0.0152
Bulk density (gm/cm³ ± SD)		0.723 ± 0.01	0.765 ± 0.006	0.715 ± 0.007
Tapped density (gm/cm³ ± SD)		0.822 ± 0.018	0.861 ± 0.007	0.828 ± 0.008
Carr's index (% ±SD)		12.03 ± 395	11.188 ± 0.042	13.589 ± 1.749
Hausner ratio (±SD)		1.134 ± 0.041	1.126 ± 0.005	1.345 ± 0.022

UMZG: Unmodified Ziziphus Gum; M1ZG: Modified Ziziphus gum by heating; M2ZG: Modified Ziziphus Gum by freeze-drying, DCM: dichloromethane; cps: centipoise.

Table 4
Precision results for Glimipride, Loratadine, and Furosemide.

	GLM				LOR				FUR			
Intra-day	Conc. µg/ml	SD	% RSD	% Rec.	Conc. µg/ml	SD	% RSD	% Rec.	Conc. µg/ml	SD	% RSD	% Rec.
	4	0.001	0.5	100.1	3	0.002	0.6	102.3	3	0.002	0.6	100.3
	6	0.006	1.5	98.0	4	0.002	0.6	102.2	4	0.002	0.4	99.9
	8	0.002	0.4	100.1	5	0.002	0.4	100.6	5	0.009	1.6	101.0
Inter-day	Conc. µg/ml	SD	% RSD	% Rec.	Conc. µg/ml	SD	% RSD	% Rec.	Conc. µg/ml	SD	% RSD	% Rec.
	4	0.002	0.7	101.3	3	0.003	1.1	102.3	3	0.003	0.9	100.5
	6	0.003	0.9	98.0	4	0.005	1.5	101.5	4	0.001	0.2	100.2
	8	0.001	0.1	99.8	5	0.007	1.9	101.9	5	0.006	1.0	100.1

Table 5
Accuracy and sensitivity results for Glimipride, Loratadine, and Furosemide.

		GLM			LOR			FUR		
Accuracy	Conc. µg/ml	10.8 (80%)	12 (100%)	13.2 (120%)	5.4 (80%)	6 (100%)	6.6 (120%)	5.4 (80%)	6 (100%)	6.6 (120%)
	SD	0.001	0.003	0.002	0.001	0.003	0.001	0.00	0.00	0.00
	% Rec.	98.84	98.40	98.87	101.7	100.6	99.32	100.7	99.10	100.37
	% RSD	0.093	0.422	0.266	0.239	0.670	0.204	0.00	0.45	0.16
Sensitivity	LOD	0.191			0.092			0.076		
	LOQ	0.637			0.307			0.253		

ibration curves with R^2 of 0.9997, 0.9997, 0.9998 for GLM, LOR, and FUR respectively.

3.2.2. Precision, accuracy, and sensitivity of the method

Tables 4 and 5 below show the results of precision, accuracy, and sensitivity. Both intraday and interday variations indicated a recovery between 98 and 102.3% for all drugs. The highest % RSD was found at 1.9%. Accuracy of the methods used was also indicated in Table 5, % recovery in the range of 98.4–101.7% was obtained for all drugs. LOD for GLM, LOR, and FUR was found at 0.191, 0.092, and 0.076 µg/ml respectively while LOQ for GLM, LOR, and FUR were found 0.637, 0.307, and 0.243 respectively.

Table 6
ANOVA analysis and PC% for solubility fold of solid dispersion formulations in aqueous media.

Source	Sum of squares	df	Mean square	F value	p-value Prob > F	PC%
Block	0.62	1	0.62			
Model (significant)	6085.9	8	760.74	1058.58	< 0.0001	
A-Drug type	3127.92	2	1563.96	2176.29	< 0.0001	37.5
B-Polymer mod.	844.7	2	422.35	587.71	< 0.0001	0.0
C-SD method	935.89	2	467.94	651.16	< 0.0001	1.5
D-Drug: Polymer ratio	1177.39	2	588.69	819.18	< 0.0001	5.5
Residual	5.75	8	0.72			55.5
Cor Total	6092.26	17				100.0

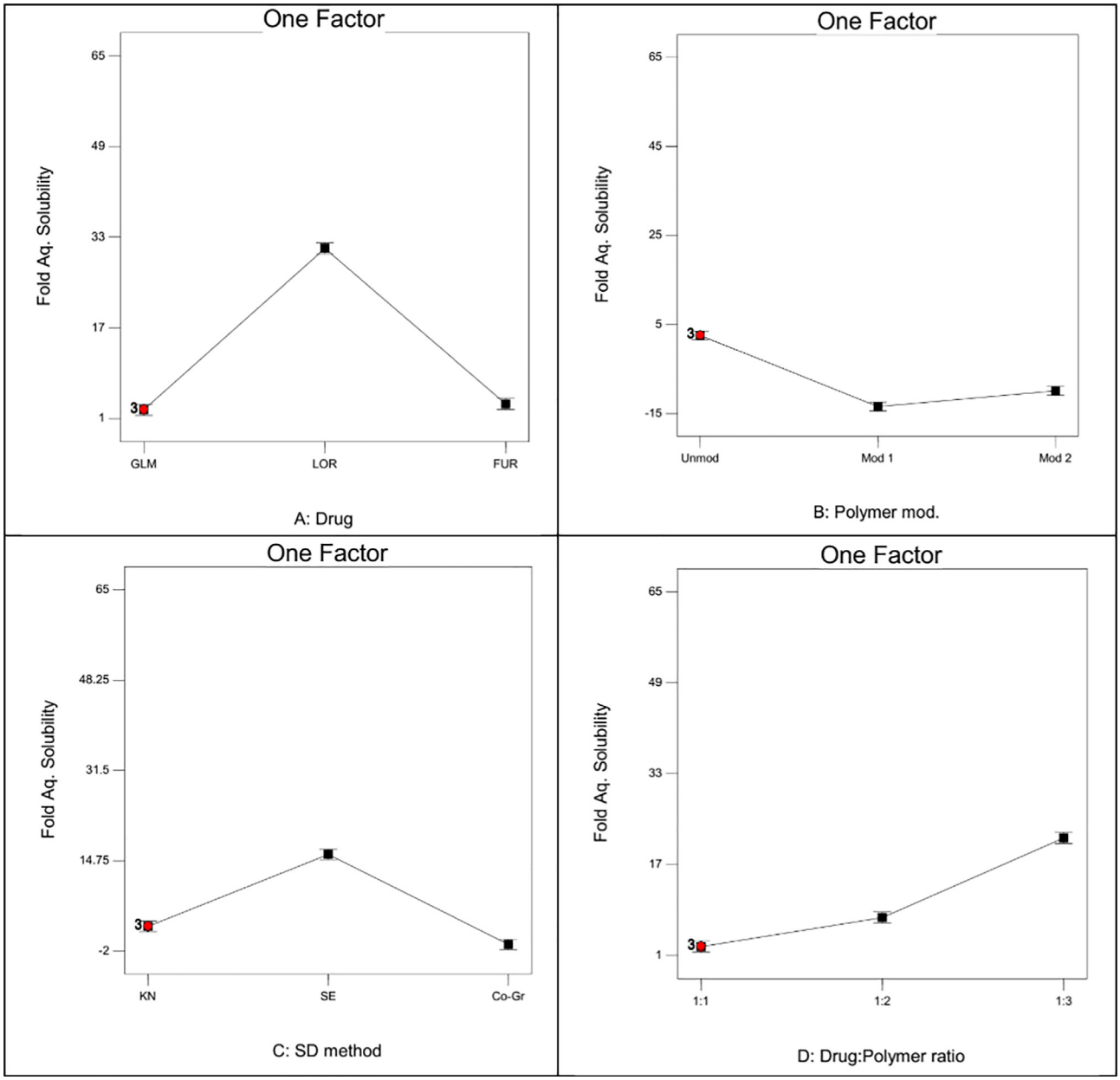

Fig. 1. Graphic model for solubility fold of solid dispersion formulations in aqueous media.

3.3. ANOVA analysis and PC% according to Taguchi model

3.3.1. Influence of the drug type on the solubility fold

As shown in Table 6 , the drug type was found significant when investigated in the TOA design for the solubility fold in different media (p-value < 0.0001). As shown in the graphic TOA model (A) in Figs. 1-5, LOR showed a higher solubility than FUR and GLM in aqueous media with pH 6.8 and 7.4, while GLM in medium with pH 1.2 showed the highest solubility. FUR showed poor solubility in all media investigated. LOR as a weakly basic drug with a pKa value of 5.52 was very soluble in an acidic medium. As shown in Fig. 7, reduced solubility at pH 1.2 was noticed when incorporated into ZG polymer as SDs. On the other hand, GLM as a weakly acidic drug with a pKa value of 8.07 showed 6 times higher solubility in an acidic medium, while FUR as a weakly acidic drug with pka 3.48 showed no change in solubility with a change in the pH value of the medium. These results suggest that ZG, as a carrier with an acidic nature (pH 4.24–4.26), showed a different degree of uptake of the tested drugs according to their physicochemical properties. These results revealed that ZG showed an interesting improvement in the solubility of the basic drug in an alkaline medium, which can greatly improve its absorption from the small intestine and bioavailability. With acidic drugs, ZG showed a different degree of modulation depending on the pka of the drug, with drugs with high pka the solubility increased in acidic medium and decreased in alkaline medium, while no effect was observed with drugs with low pka. The possible mechanisms responsible for the ZG modulation of drug solubility could be the change in crystal size, the solubility effect of the polymer and the polymer hybrids, the presence or absence of aggregation of drug crystallites, the wettability and dispersibility of the drug from the dispersion, the degree of dissolution of the active ingredient in the polymer matrix and the solid-state conversion of the active ingredient particles **(**Khan et al., 2004; Popović, Čakar and Agbaba, 2009; Frizon et al., 2013**).**

3.3.2. Influence of the polymer modification on the solubility fold

As shown in Table 7, the polymer modification as a factor investigated in the TOA design for the solubility fold in different media is significant (p-value < 0.0001). As shown in the graphic TOA model (B) in Figs. 1-5, the modification of ZG was found to result in different physicochemical properties that affect its modulation

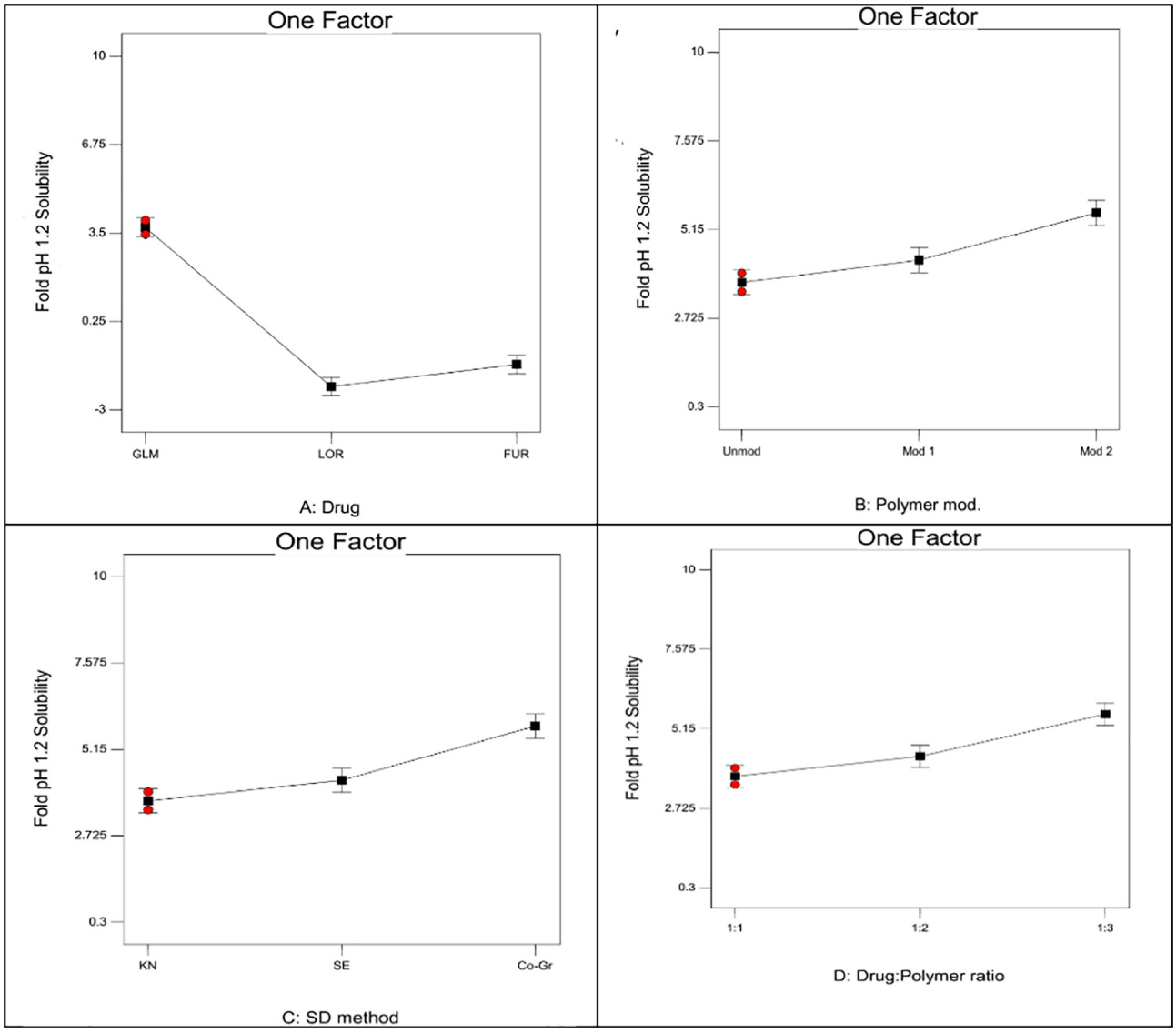

Fig. 2. Graphic model for solubility fold of solid dispersion formulations in pH 1.2.

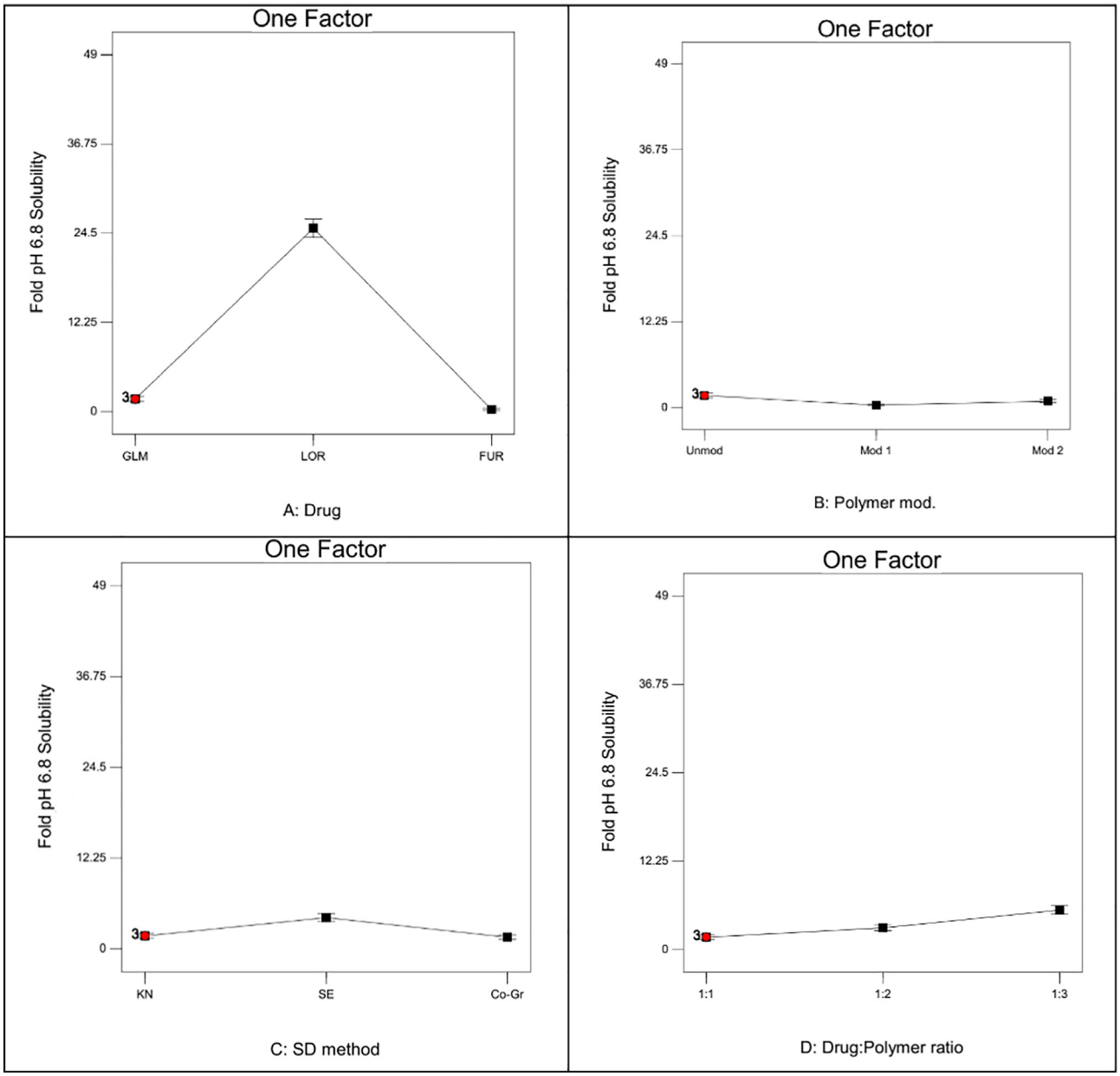

Fig. 3. Graphic model for solubility fold of solid dispersion formulations in pH 6.8.

of drug solubility. Unmodified ZG showed a higher solubility in aqueous media with pH 7.4, while modification by freeze-drying or heating showed a higher solubility in pH 1.2. The modification of ZG by freeze-drying showed a better improvement in solubility in various media investigated than the modification by heating. Modified and unmodified forms of ZG showed no significant difference in solubility improvement at pH 6.8. These results can be attributed to the type of crosslinking that could be induced in ZG by modification and to the sustaining effect that could be produced. ZG showed the highest viscosity and swelling index by heat modification, while modification by freeze-drying increased the viscosity slightly and even decreased the swelling index of ZG. The high solubility improvement in modified ZG in the acidic medium could be attributed to the nature of the bonds created in it by crosslinking as acidic polymers, which were weak in an acidic environment with no lasting effect. It seemed that the stronger crosslinking and a good preservation effect through modification of ZG in neutral and alkaline media, i.e., pH-dependent effect, can be achieved (Ofridam et al., 2021).

3.3.3. Influence of the SD method on the solubility folding in different media

As shown in Table 8, the method for the production of SD as a factor investigated in the TOA design for the solubility fold in different media was found significant (p-value < 0.0001). As shown in the graphic TOA model (C) in Figs. 1-5, the solvent evaporation process showed the highest solubility in various media except at pH 1.2 where the co-grinding process had the greatest effect on solubility. These results could be attributed to the different mixtures formed after the dispersion of drug molecules and ZG and the degree of their incorporation into the polymer matrix, which affect the degree of wettability and improved solubility. Among

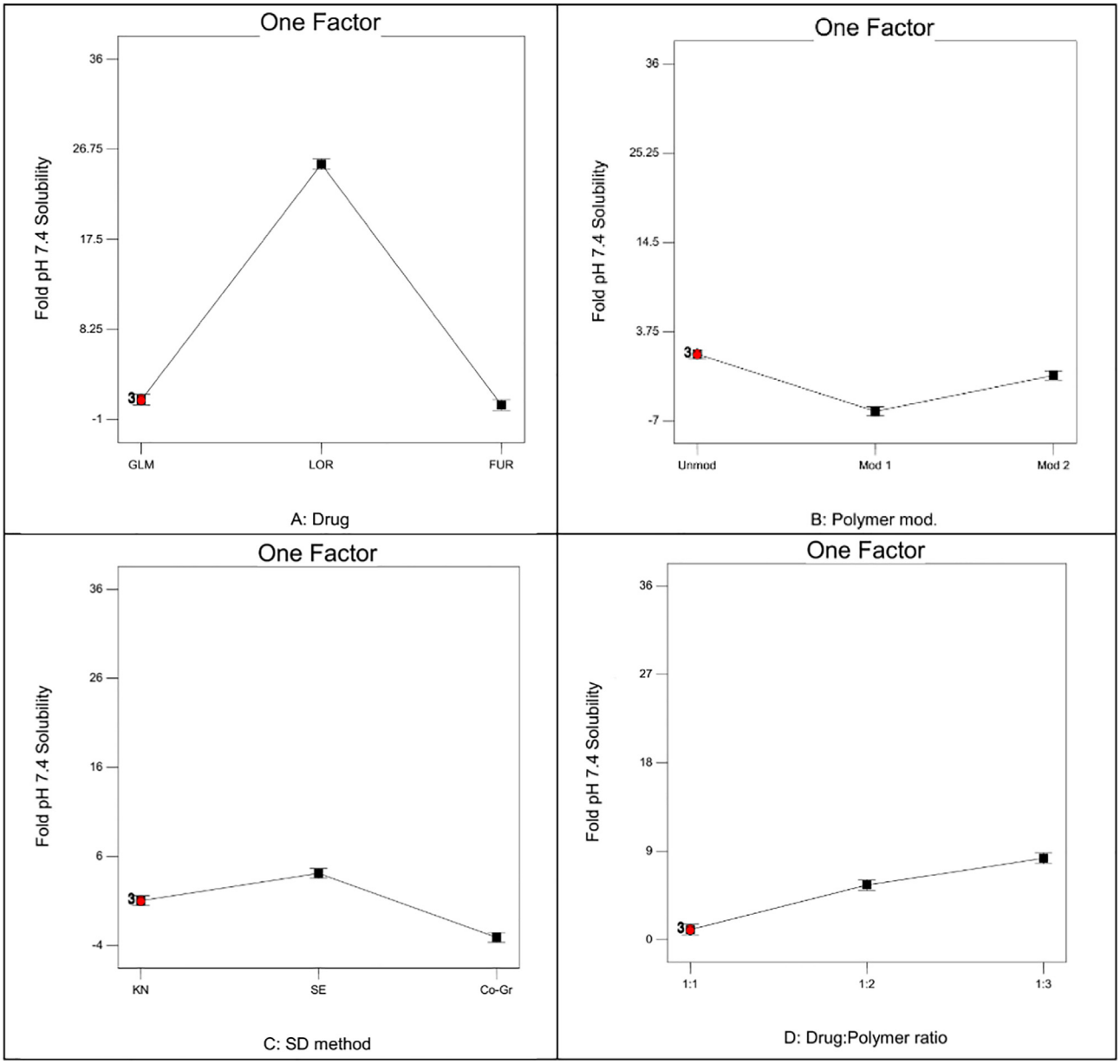

Fig. 4. Graphic model for solubility fold of solid dispersion formulations in pH 7.4.

the various methods used in the preparation of solid mixtures, solid dispersions gave higher solubility than any method which had properties such as ease of preparation, reliability of the process, avoidance of the use of organic solvents or high temperatures, and less cumbersome; Techniques like kneading and co-grinding techniques seem to be the simpler and most convenient method from a practical point of view (Babu, Prasad and Murthy, 2002).

3.3.4. Influence of the Drug/polymer ratio on the solubility fold in different media

As shown in Table 9, the drug/polymer ratio in the prepared SDs as a factor investigated in the TOA design for the solubility fold in different media was found significant (p-value < 0.0001). As shown in the graphic TOA model (D) in Figs. 1-5, increasing the ratio of ZG to the drug tested in the SDs produced will increase the solubility in various media many times. As previously reported, increasing the amount of carrier in SD offers the chance of absorbing all drug molecules and thus increasing the effect of solubilization (Papageorgiou et al., 2006; Akiladevi et al., 2011).

3.3.5. Percentage contribution PC% of factors examined

As shown in Tables 6-10 above, the percentage contribution of the four factors examined indicated that the type of drug used made the highest contribution to the solubility fold results in all of the media examined. A higher solubility was observed in acidic and alkaline media than in water. It is known that the physicochemical properties of the drug and the nature (Acidic/ Basic) of the carrier in solid dispersion determine its degree of solubility in the solvent. The second factor that varied depending on the type of medium was the ratio of drug to ZG. The method of making SD and the type of modification of ZG showed a lower proportion of the contribution (Akiladevi et al., 2011).

3.3.5.1. Formulation optimization. Table 11 shows the top five optimized formulations selected according to the TOA model. Formula with modified ZG by freeze-drying, LOR as a model drug, a drug to

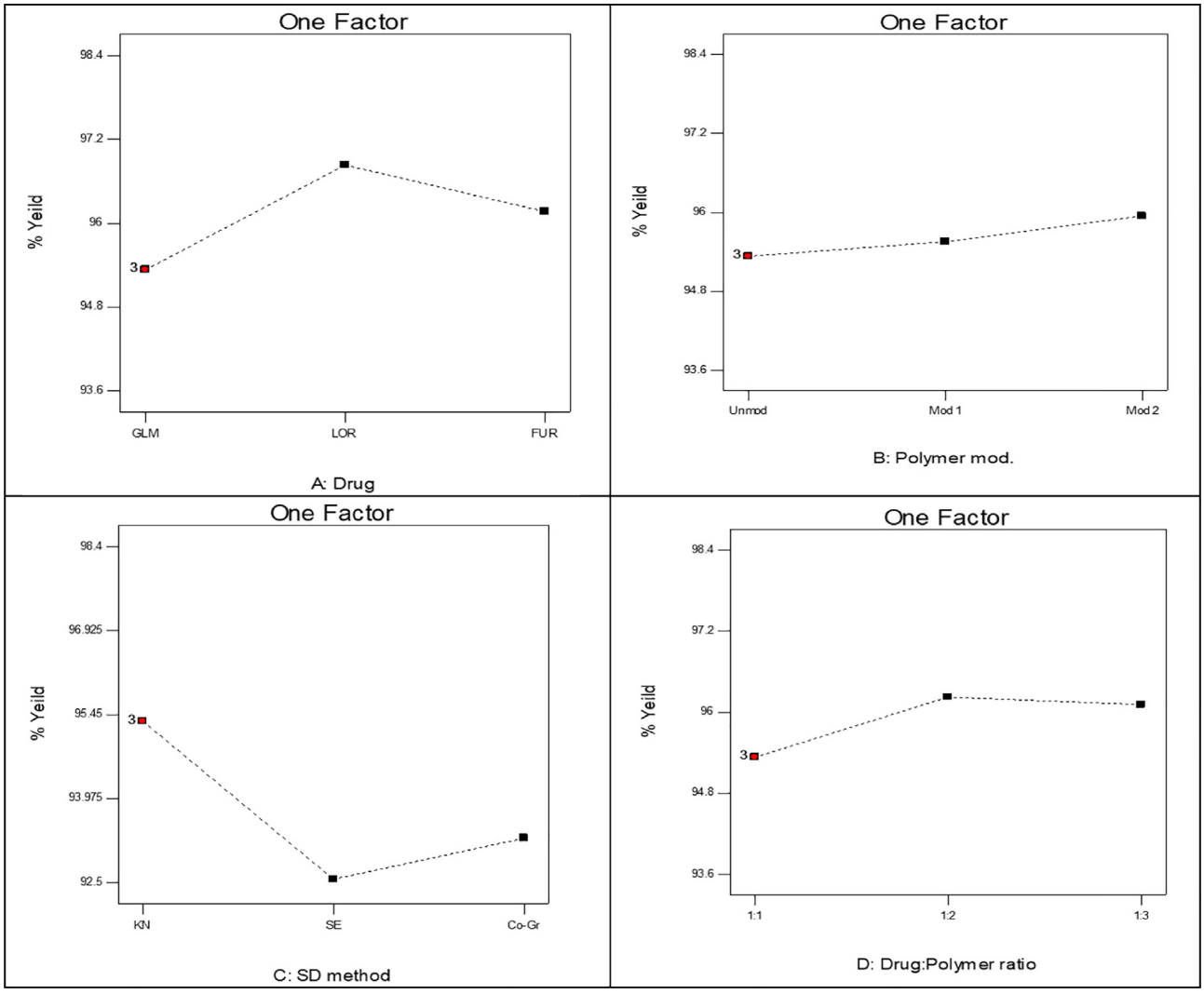

Fig. 5. Graphic model for percentage yield of solid dispersion formulations.

Table 7
ANOVA analysis and PC% for solubility fold of solid dispersion formulations in pH 1.2.

Source	Sum of squares	df	Mean square	F value	p-value Prob > F	PC%
Block	0.077	1	0.077			
Model (significant)	157.3	8	19.66	225.62	< 0.0001	
A-Drug type	120.68	2	60.34	692.4	< 0.0001	69.6
B-Polymer mod.	11.3	2	5.65	64.82	< 0.0001	0.1
C-SD method	14.1	2	7.05	80.89	< 0.0001	1.8
D-Drug: Polymer ratio	11.22	2	5.61	64.38	< 0.0001	0.0
Residual	0.7	8	0.087			28.5
Cor Total	158.07	17				100.0

Table 8
ANOVA analysis and PC% for solubility fold of solid dispersion formulations in pH 6.8.

Source	Sum of squares	df	Mean square	F value	p-value Prob > F	PC%
Block	0.042	1	0.042			
Model (significant)	76.17	8	9.52	792.25	< 0.0001	
A-Drug type	68.96	2	34.48	2869.09	< 0.0001	88.4
B-Polymer mod.	1.59	2	0.79	65.94	< 0.0001	0.0
C-SD method	2.4	2	1.2	99.88	< 0.0001	1.1
D-Drug: Polymer ratio	3.22	2	1.61	134.09	< 0.0001	2.1
Residual	0.096	8	0.012			8.3
Cor Total	76.31	17				100.0

Table 9
ANOVA analysis and PC% for solubility fold of solid dispersion formulations in pH 7.4.

Source	Sum of squares	df	Mean square	F value	p-value Prob > F	PC%
Block	0.11	1	0.11			
Model (significant)	2857.8	8	357.23	1560.78	< 0.0001	
A-Drug type	2394.8	2	1197.4	5231.64	< 0.0001	78.7
B-Polymer mod.	145.69	2	72.84	318.27	< 0.0001	0.0
C-SD method	156.18	2	78.09	341.19	< 0.0001	0.4
D-Drug: Polymer ratio	161.13	2	80.57	352.01	< 0.0001	0.5
Residual	1.83	8	0.23			20.4
Cor Total	2859.74	17				100.0

Table 10
ANOVA analysis and PC% for percentage yield of solid dispersion formulations.

Source	Sum of squares	df	Mean square	F value	p-value Prob > F	PC%
Block	0	1	0			
Model (significant)	35.66	8	4.46	6.37E + 07	< 0.0001	
A-Drug type	6.77	2	3.39	6.37E + 07	< 0.0001	15.8
B-Polymer mod.	1.15	2	0.57	6.37E + 07	< 0.0001	0.0
C-SD method	24.92	2	12.46	6.37E + 07	< 0.0001	66.7
D-Drug: Polymer ratio	2.82	2	1.41	6.37E + 07	< 0.0001	4.7
Residual	0	8	0			12.9
Cor Total	35.66	17				100.0

Table 11
Analysis of 5 combinations of categoric factor levels according to the TOA model.

No.	Drug	Polymer mod.	SD method	D:P ratio	Sol. Fold Aq.	Sol. Fold pH 1.2	Sol. Fold pH 6.8	Sol. Fold pH 7.4	% Yield	Desirability	
1	LOR	Mod2	SE	1:3	51.1	2.2	41.4	33.0	95.4	0.7	Selected
2	LOR	Mod2	KN	1:3	37.7	1.6	32.4	29.9	98.2	0.7	
3	LOR	Unmod	CG	1:3	46.8	1.8	35.8	28.3	95.6	0.6	
4	LOR	Mod2	CG	1:3	34.4	3.7	31.7	25.8	96.2	0.6	
5	LOR	Mod1	SE	1:3	47.5	0.9	36.7	28.6	95.1	0.6	

SD: Solid Dispersion, D: Drug, P: Polymer, Sol.: Solubility, Mod1: Modified Ziziphus gum by heating, Mod2: Modified Ziziphus gum by freeze-drying, Unmod: Unmodified Ziziphus gum, LOR: Loratadine, SE: Solvent Evaporation method, KN: Kneading method, CG: Co-Grinding method.

polymer ratio 1: 3, and solvent evaporation process for SD manufacture was selected as the optimized formula. The predicted and actual values of the responses are given in Table 12. There was no difference between the values indicating the validity of the design used for this study.

3.4. Equilibrium solubility studies and solubility fold

SDs were evaluated for equilibrium solubility (g /ml) in distilled water and media of pH 1.2, pH 6.8, and pH 7.4. The results were shown in Figs. 6-8. Fig. 6 showed that increasing drug/polymer ratio and using modified ZG such as (SD2 and SD3) will increase the aqueous solubility of GLM by two folds compared to GLM pure, while the solubility of SD3 at pH 1.2 was twice that of SD1 And SD2. This may be due to the amorphous state of each. The solubility fold of GLM at pH 6.8 was also improved twice in SD3 and SD2 compared to SD1. The solubility fold of GLM improved slightly at pH 7.4. Solubility of pure GLM was found as follows pH 7.4 > pH 6.8 > water > pH 1.2. The equilibrium solubility of GLM was improved when mixed with M1ZG and M2ZG. The solubility folds of LOR at pH 1.2 were reduced in SDs, which may be due to the pH of the polymer, which affects the solubility of the drug. The solubility of pure LOR in an acidic medium was very high due to the nature of LOR, which dissolves in an acidic medium, while the solubility in water, pH 6.8 and pH 7.4, was very low. The solubility of LOR SDs was thus improved as follows water > pH 6.8 > pH 7.4. This is due to the increase in the polymer content leading to a decrease in the pH of the medium.

Fig. 8 shows the results of the solubility folds of FUR. Solubility folds were improved in water as follows SD8 > SD7 > SD6, which can be attributed to the increase in the polymer ratio. The solubility folds of FUR at pH 6.8 and pH 7.4 were nearly identical and slightly reduced in SDs compared to pure FUR, which may be due to the pH of the polymer, which affects the solubility of the drug. The solubility of pure FUR in an alkaline medium was very high due to the nature of FUR, which dissolves in an alkaline medium. The solubility of FUR SDs has thus been improved depending on the pH as follow water > pH 6.8 > pH 7.4 and depending on the type

Table 12
Comparison between predicted saturation solubility results from Taguchi model and solubility of the actual formula.

Media	Water	pH 1.2	pH 6.8	pH 7.4
Predicted solubility	51.1	2.2	41.4	33.0
Actual solubility	52.6 ± 0.7	0.5 ± 0.01	43.9 ± 0.49	31.7 ± 0.10

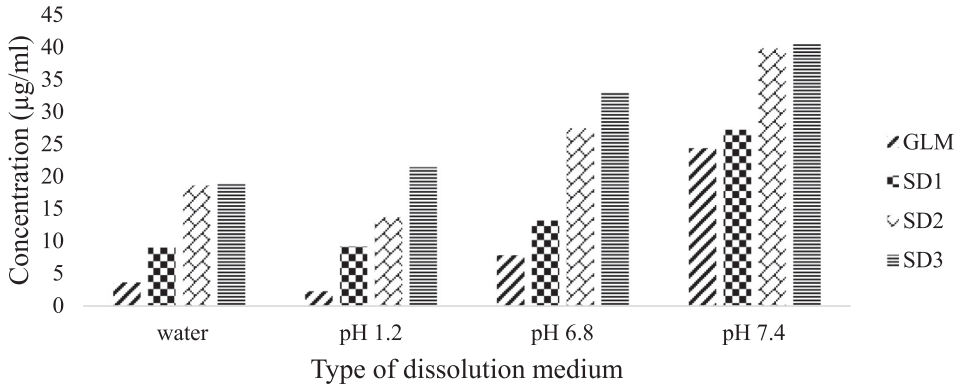

Fig. 6. Solubility of GLM and its solid dispersion in different media.

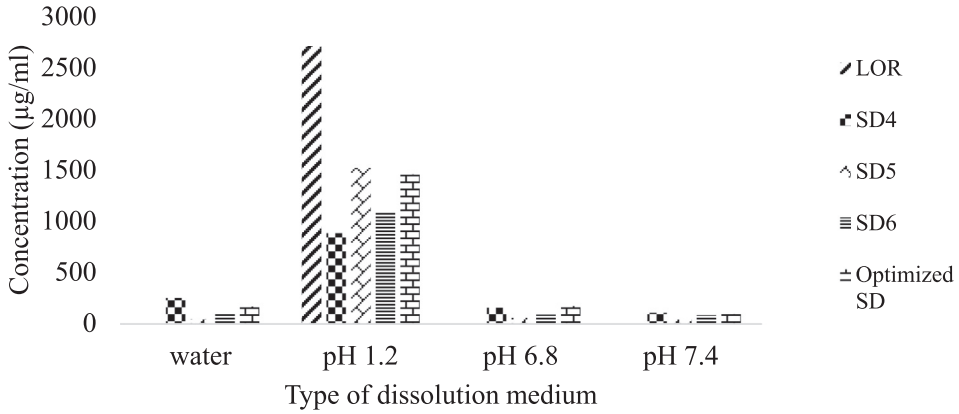

Fig. 7. Solubility of LOR and its solid dispersion in different media.

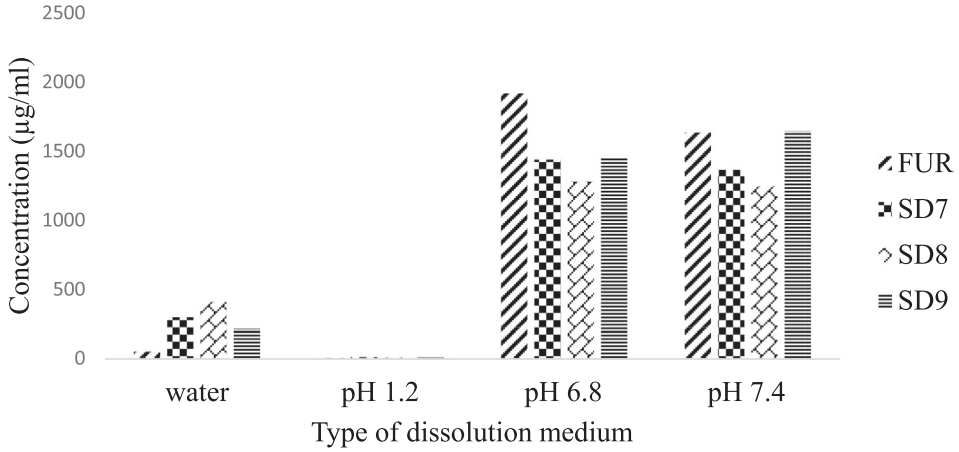

Fig. 8. Solubility of FUR and its solid dispersion in different media.

of mixtures SD8 > SD7 > SD6, and this is due to the increased ratio of the polymers that lead to a lowering of the pH value of the dissolved media (Ofridam et al., 2021).

3.5. Percentage yield

As shown in Fig. 9, the % practical yield was found in the range of 93.7–98.3%. All factors studied in the TOA design were found significant (p-value < 0.0001) on the percentage yields. The percentage contribution was found as follows, SD preparation method > type of drug > ratio of drug to polymer > method of modification of ZG. The method of choice for the highest percentage yield was the kneading process, then the co-grinding, and finally the solvent evaporation process. These results could be due to the nature of the drug's uptake in ZG. LOR showed the highest percentage recovery while GLM was the lowest. This result may be due to the nature of the drug, a weakly basic drug can be incorporated into ZG more than an acidic one, since ZG is an acidic polymer that can improve

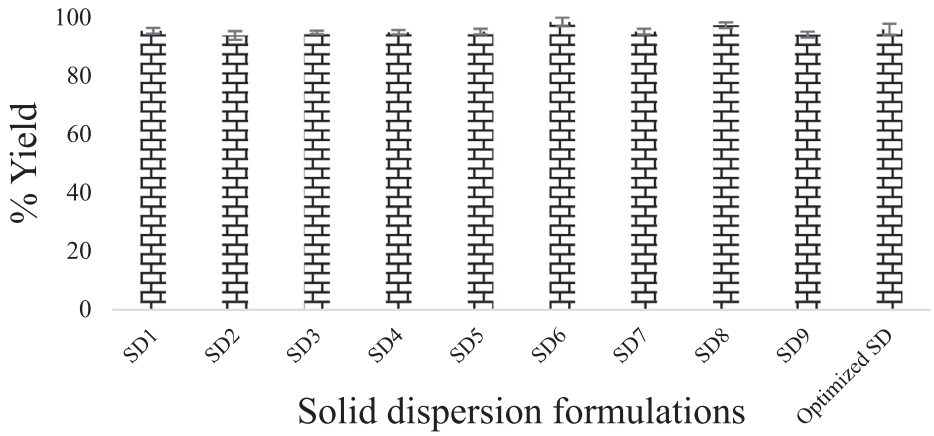

Fig. 9. % Practical yield of solid dispersion formulations.

its solubility and dispersion in the polymer matrix. The lowest ratio (1: 1) between drug and ZG showed the lowest percentage recovery while the ratio of (1: 2) showed the highest recovery. Increasing the ratio up to 1: 3 showed no significant difference in the percentage yield. The modification of ZG by the two methods, heating, and freeze-drying, showed significant differences in the percentage yield. The modification by freeze-drying showed the highest percentage yield. These results were similar to those obtained by Zaghloul *et al* in their study on Silica/Chitosan for improving the solubility of Terconazole **(**Zaghloul et al., 2022**).**

3.6. Fourier transform Infrared spectroscopy (FTIR) studies:

FTIR analysis was performed to exclude chemical interactions between ZG and drugs used. FTIR demonstrates the presence of various functional groups. The FTIR spectrum of glimipride, loratadine, furosemide, unmodified ZG polymer, M1ZG polymer, M2ZG, and various mixtures are shown in the diagram (Figs. 10-12). The FTIR spectrum of GLM shows characteristic peaks at 3367 cm-1 because of the NH stretching, at 3288 cm-1 because of the OH stretching, at 1707 cm-1 because of the C = O stretching, at 1670 cm-1 because of the C = C stretch, at 1350 cm-1 due to the OH bend, at 1159 cm-1 due to the CO stretch, at 883 cm-1 due to the C = C bend. The FTIR spectrum of the LOR shows characteristic peaks at 2985 cm-1 due to the CH stretching, at 1701 cm-1 due to the C = O stretching, and 1570 cm-1 due to the cyclic alkene (C = C stretching) 1430 cm-1 due to carboxylic acid (OH bend), at 1103 cm-1 due to CO stretching and at 993 cm-1 due to C = C bend. The FTIR spectrum of FUR shows characteristic peaks at 3398 cm-1 due to the OH stretching, at 2550 cm-1 due to the SH stretching, at 1824 cm-1 due to the CH bend (aromatic compound), at 1674 cm-1 due to C = O stretching, at 1409 cm-1 due to S = O stretching, at 1261 cm-1 due to CO stretching (alkyl aryl ether), at 707 cm-1 due to C = C bending. FTIR spectrum from Unmod. ZG showed OH stretch at 3419.79 cm-1, CH stretch at 2931.8 cm-1, C = C stretch at 1622.13 cm-1, OH flexion at 1417.68 cm-1 and S. = O stretch

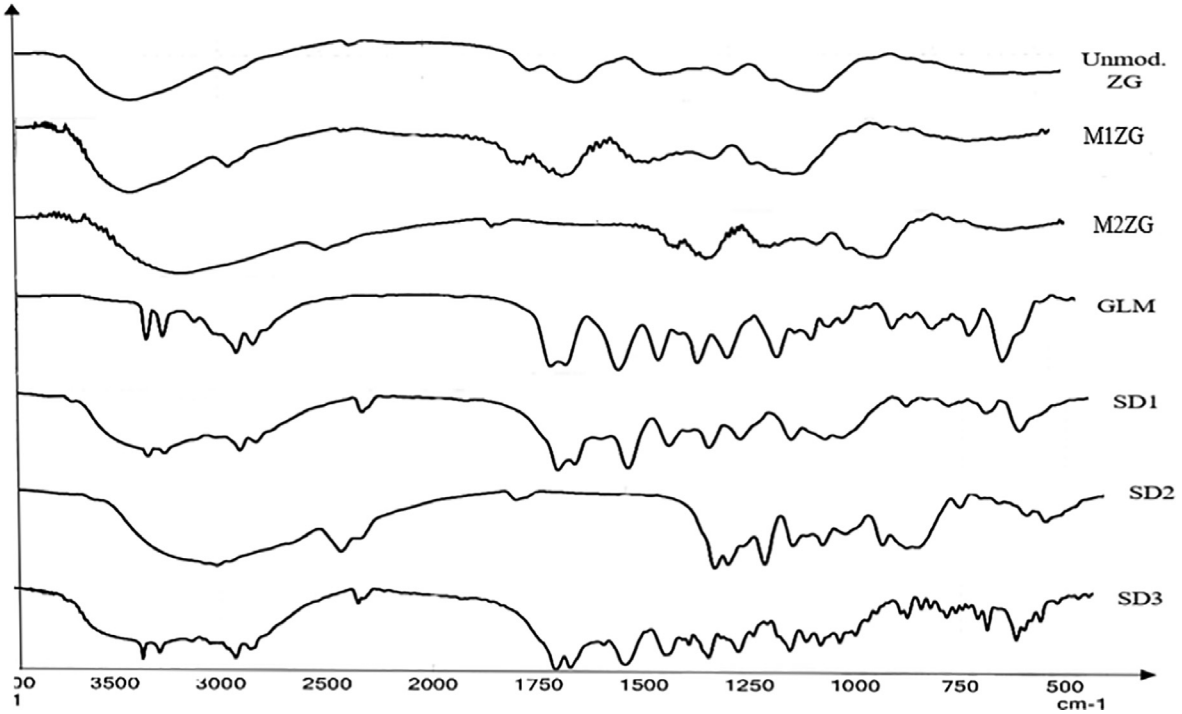

Fig. 10. FTIR of GLM and its solid dispersions.

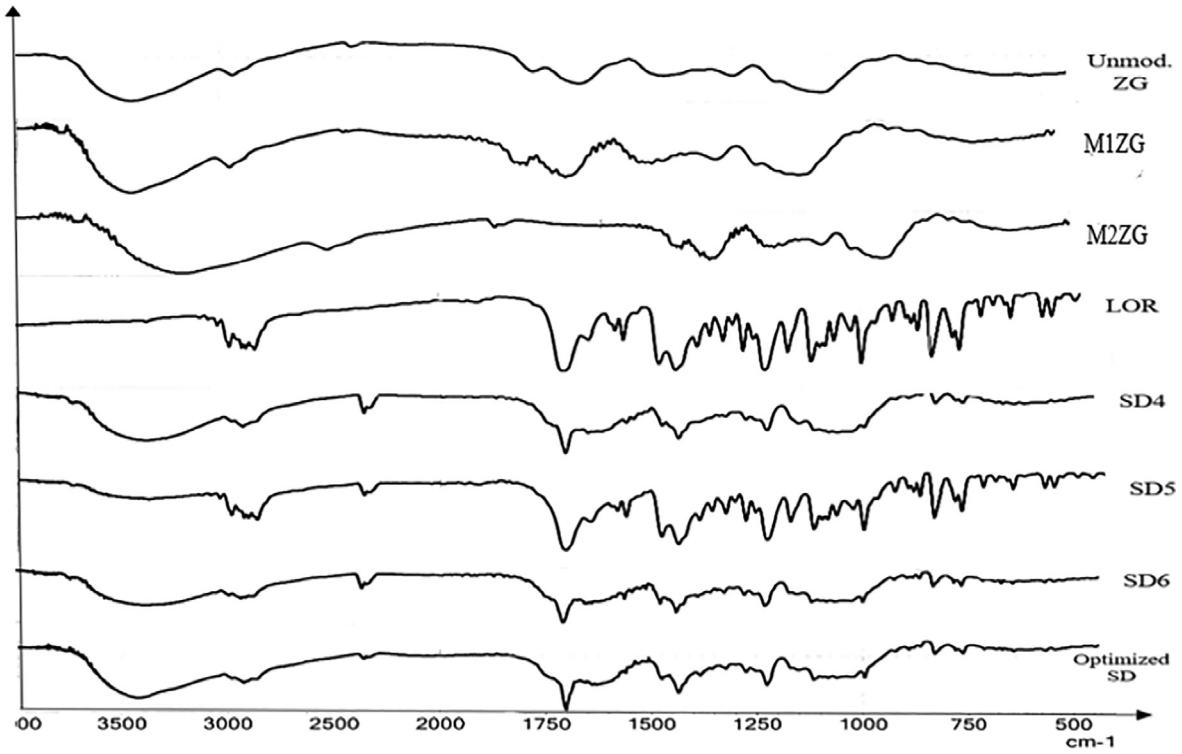

Fig. 11. FTIR of LOR and its solid dispersions.

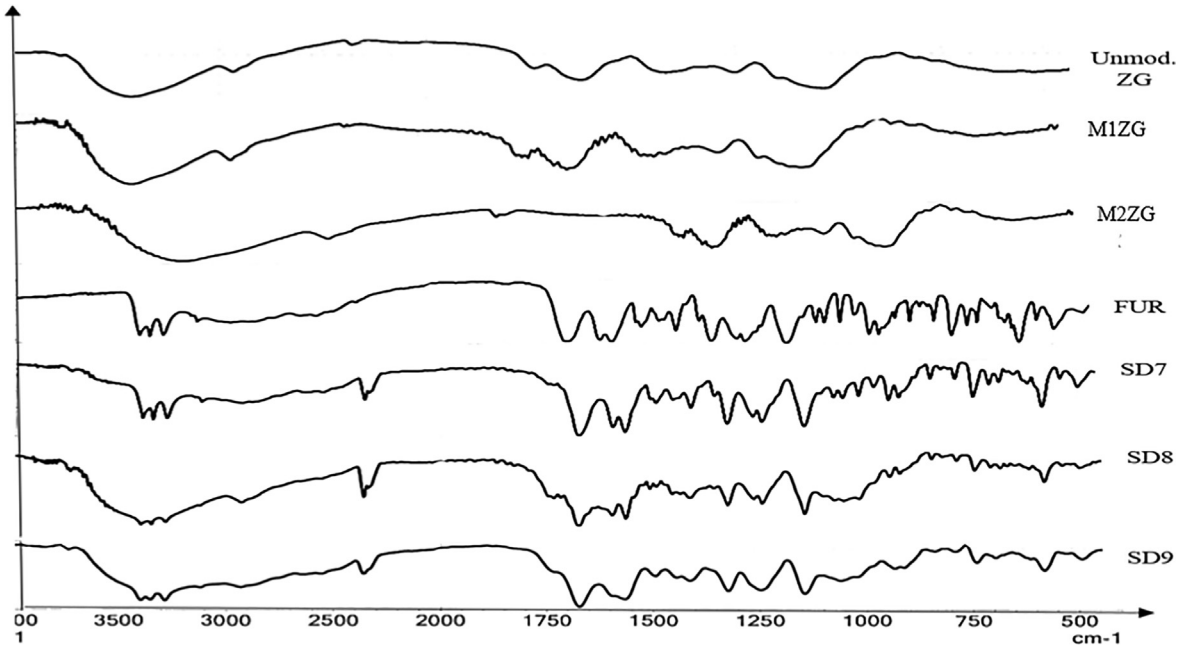

Fig. 12. FTIR of FUR and its solid dispersions.

at 1033.85 cm-1. The FTIR spectrum of M1ZG showed OH stretching at 3421.72 cm-1, CH stretching at 2929.87 cm-1, C = C stretching at 1621.13 cm-1, and S = O stretching at 1031, 92 cm-1. The FTIR spectrum of M2ZG showed OH stretching at 3421.72 cm-1, CH stretching at 2929.87 cm-1, C = C stretching at 1622.13 cm-1, and S = O stretching at 1035, 77 cm-1. The presence of almost all of the characteristic peaks of drugs and polymers in the spectra of all solids produced could not indicate any chemical interaction of the drug with the polymer. The presence of polymers in the blends showed some degree of overlapping and brooding peaks, which may indicate some physical interactions.

4. Conclusion

The use of natural excipients represents a good alternative to synthetic ones in the manufacture of pharmaceuticals. This study revealed that the polymer extracted from *Ziziphus spina-christi*

and its modifications could be used to modulate the aqueous solubility of poorly soluble drugs and hence their bioavailability. This study revealed no chemical interactions between ZG and drugs used. The optimized formula showed an enhanced aqueous solubility of Loratadine by 51 folds. The method of preparing solid dispersions using ZG as a carrier greatly influenced the incorporation of the drug molecules and the amount that could be loaded into the polymer matrix. The obtained results are encouraging for the preparation of dosage forms followed by more *in vitro* and *in vivo* studies as well as stability studies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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