Natural Carrier-Mediated Solubility Enhancement Of Poorly Water-Soluble Drug

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Abstract
Developing efficient strategies to enhance the solubility of poorly water-soluble drugs is crucial for their successful formulation and delivery. Natural carriers offer a promising approach for this purpose, leveraging their inherent biocompatibility and the ability to modulate drug-solvent interactions through non-covalent complexation. This abstract explores the concept of utilizing natural carriers for solvent evaporation, a widely employed technique for solubility enhancement. We discuss the mechanisms by which natural carriers can improve drug solubility during solvent evaporation and the various factors influencing their efficacy. Recent advancements in natural carrier design and their integration with solvent evaporation for solubility enhancement are highlighted. The natural carrier used are zizipus spina christi gum and locust bean gum. The Rhamnaceous family, which includes the genus Ziziphus, has over 100 species of deciduous or evergreen trees and shrubs that are found worldwide in tropical and subtropical climates. Finally, the future perspectives and potential challenges associated with this approach are addressed.

Keywords: Box-Behnken design, Design expert, Locust bean gum, Solid dispersion, Solvent Evaporation

Introduction

Due to its ease of use, patient compliance, minimal sterility limitations, affordability, and dose flexibility, oral administration is among the most accepted modes of administration. Consequently, several pharmaceutical firms are working to create and manufacture more oral bioequivalent drugs.[1] A major obstacle in the realm of pharmaceutical research is the production of poorly soluble drugs, commonly referred to as poorly water-soluble or poorly bioavailable pharmaceuticals. These drugs exhibit poor solubility in aqueous solutions, which may hinder their absorption and, as a result, reduce their therapeutic efficacy.[2] However, up to 90% of the novel chemical entities and around 40% of the commercially available oral dose formulations have low water solubility.[3] Biopharmaceutics classification system (BCS) class II medications,such as phenytoin, danazol, and nifedipine, and BCS class IV pharmaceuticals, such as furosemide, domperidone, and hydrochlorothiazide, are examples of drugs with poor solubility. Before a drug maybe absorbed when taken orally in a solid dosage form—such as a tablet, capsule, or suspension—it must dissolve in the gastrointestinal fluids and be freed from the dosage form.[4] A variety of techniques are employed to increase the solubility of medications that are poorly soluble, including complexation, co-solvency, salt formation, solid dispersion, pH adjustment, crystal engineering, decrease of particle size, and physical and chemical changes of the drug.[5]

Domperidone is chemically described as 5-chloro-1-[1-[3-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-propyl]4-piperidinyl]-1,3-dihydro-2H-benzimidazol-2-one. Domperidone is an antagonist of the dopamine (D2) receptor. It is used to treat and prevent acute nausea and vomiting, particularly from radiation and cytotoxic treatments. The half-life of elimination is 5-7 hours, and 91-93% of DOM is bound to proteins.

Furthermore, Domperidone maintains the cardiac sphincter's correct closure, preventing stomach contents from re-entering the oesophagus.[6] Domperidone is classified as a class II drugs under the Biopharmaceutical Classification System (BCS) since it is extremely permeable and weakly water-soluble. It is almost complete insoluble in water causes a 13–17% reduction in bioavailability upon oral ingestion.[7]

Many techniques have been used to increase drug candidates' solubility. Solid dispersion (SD) method is one of them that has garnered a lot of interest as an effective way to accelerate the rate of dissolution, which raises the solubility of a variety of poorly soluble in water drugs. The enhanced wettability of SDs has been linked to quick and efficient drug breakdown, enhanced drug particle dispersibility, presence of the drug in an amorphous state with enhanced solubility, and lack of drug particle aggregation employing different hydrophilic carriers.[8] Polymer carriers are often classified as either entirely synthetic or natural polymers. Polyethylene glycol (PEG), polyvinyl pyrrolidone (PVP), and polymethacrylates are examples of synthetic polymers. In the meanwhile, natural polymers are made up of cellulose derivatives (such as hydroxypropyl methylcellulose, ethyl cellulose, and hydroxypropyl cellulose) or starch derivatives (such as cyclodextrins).[9] Solvent removal at low temperatures and regulated rates can be achieved using vacuum evaporation. Utilising an azeotropic solvent combination in water can help get over the challenges associated with choosing a common solvent for both the medication and the carrier.[10]

A novel avenue for increasing the solubility of hydrophobic drugs has been made possible using natural extract materials as drug carriers. Loading a hydrophobic drug onto a high surface area carrier significantly increased its solubility. When compared to synthetic carriers, natural carriers—which come from things like proteins, polysaccharides, and plant extracts—often offer a more ecologically responsible and sustainable alternative. Their innate qualities, including their antibacterial or antioxidant activity, may also offer further advantages, enhancing the finished product's usefulness.[11]
The Rhamnaceae family, which includes the genus Ziziphus, has over 100 species of deciduous or evergreen trees and shrubs that are found worldwide in tropical and subtropical climates. The plant typically develops into a tree, but heavy grazing in the latter stages of the dry seasons sometimes causes it to take on the shape of a shrub.[12]

Fig. 1: Ziziphus spina Christi gum

Locust bean gum (LBG) is a neutral polymer made up of galactose and mannose units; as such, it falls within the galactomannan category. In the biopharmaceutical industry, this natural polymer is gaining more attention, especially for oral medication administration. The carob tree (Ceratonia siliqua), which is native to various parts of North Africa, South America, and Asia, is the source of locust bean gum. It is most found in the Mediterranean region.[13]

Fig. 2: Locust bean gum

Materials and Methods

Materials

Ziziphus spina-christi fruits were brought over from the nearby market. The pure drug Domperidone was purchased from Torrent Pharmaceuticals Ltd Pithampur. Locust bean gum was obtained from Triveni Chemicals, Vapi, Gujarat, as a gift sample. All other reagents were found to be of analytical grade.

Methods

Extraction of Ziziphus gum polymer

Ziziphus spina-christi fruits were crushed after being cleaned with water to get rid of dirt. The crushed fruit material was refrigerated for 72 hours while it was soaked in an excessive amount of distilled water. After physically separating the fruit bulb and squeezing it in a muslin bag to extract the mark, the filtrate was placed in a refrigerator and left for a full day. After that, the supernatant was removed by decantation, revealing a transparent mucilaginous solution. To precipitate the mucilage, an equivalent volume of ethyl alcohol was added to the filtrate was divided, dried at 45 degrees Celsius in an oven, ground into a fine powder, and then put through sieve No. 80 to become a light brown powder. Until it was needed again, the resulting powder was stored in a dry, amber screw-capped glass container.[14]
Modification of Ziziphus gum polymer (ZG)
The gum was heated at 120 ^{0}C in hot air oven for 2 hours.

Preparation of modified locust bean gum:

A porcelain dish containing powdered gum was heated in a hot air oven for varying lengths of time and temperatures. Finally, the obtained modified locust bean gum was sieved through 100 mesh and kept at 25°C in an airtight container.[15]

Characterization of ZG polymer and Locust Bean Gum

Swelling index:

Each ZG polymer and Locust Bean Gum was weighed precisely to the nearest gramme and then put into a 100 ml measuring cylinder. It was remarked how much powder there was at first. Next, the gum was vigorously shaken to completely distribute it in 100 millilitres of distilled water. For a whole day, the measuring cylinder was left at room temperature and humidity. After 24 hours, the volume that the ZG polymer and locust bean gum sediment
occupied was measured. The following formula was used to determine the swelling index, which was represented as a percentage:

SI¼ðX1X0=X0\x100

where: X0 represents the powder's starting height in the measuring cylinder and X1 represents the gum's swelling after a 24-hour period.

Viscosity Measurement:

Using a Brookfield LV DV, the viscosity of a 1% aqueous solution of each of the polymers UMZG, M1ZG, and locust bean gum was determined in accordance with USP requirements.

Measured at 200 rpm with a spindle 61.

Angle of repose

The funnel technique was used to calculate the angle of repose. Weighed precisely, the powder was placed in a funnel. A funnel's height was changed in this manner that its tip barely contacts the top of the powder pile. The powder was let to freely flow through the funnel and reach the top. The following formula was used to determine the powder heap's diameter and angle of repose:

Tan (θ) = H/R

H Height of powder heap

R Radius of powder heap

Compressibility index and Hausner ratio:

For every ZG polymer and powdered locust bean gum polymer, the loose bulk density and the tapped bulk density were measured. A calibrated graduated cylinder of 100 millilitres was filled with 10 grammes of powdered gum, and the initial volume was noted.

Next, using the Digital Automatic Tap Density Test Apparatus VEEGO VTAP / MATIC II (Veego Instrument Corporation, India), the cylinder was dropped onto a firm surface. Until there was no more audible change, tapping was kept up. The following formula was used to determine the Loose Bulk Density and Tapped Bulk Density:

LBD= Weight of powder/Initial volume the pack

TBD= Wight of powder/Tapping volume of pack

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

Carr's index (%) = (TBD-LBD) x 100

The Hausner ratio was determined using the following equation:

Hausner ratio TBD/LBD [16]

Table1: Characterization of Ziziphus gum polymer, Modified Ziziphus gum and Modified Locust Bean Gum

Parameters	**MZG**	**MLBG**
Swelling index (%±SD)	1783.3±76.37	284.62 ± 4.65
Viscosity (cps±SD)	20.7±0.435	418 ± 32.16
Angle of repose (^{0}±SD)	40.66±0.097	35.24 ± 2.34
Bulk Density (gm/cm3±SD)	0.765±0.006	0.50 ± 0.08
Tapped density(gm/cm3±SD)	0.861±0.007	0.63 ± 0.06

Preformulation studies

Preparation of 6.8 pH phosphate buffer solution: Dissolve 28.80 g of disodium hydrogen phosphate and 11.45 g of potassium dihydrogen phosphate in sufficient water to produce 1000 ml. The pH of the buffer solution was adjusted with the help of 1N HCl and 0.1N NaOH.

Preparation of DOM Standard Stock Solutions

Standard stock solution of DOM (100 mg) was prepared in 100 ml in phosphate buffer pH 6.8 with 0.05 % w/v SLS to get the final concentration of 1000 µg/ ml.

Preparation of DOM Working Solution

Aliquots of stock solution were further diluted with phosphate buffer pH 6.8 with 0.05% SLS solution to get working solution of 2, 4, 6, 8 and 10µg/ml and the working standards were scanned through UV spectroscopy.

Determination of λmax

The standard solution of DOM (6 µg/ml) was scanned in the wavelength region of 200-400 nm and the λmax was found to be 284 nm.[17]

Bulk Density
The volume of each pore in the sample is included in the bulk density measurement. Precisely, starting volumes (V) were measured after weighted amounts of powder (M) were accurately placed into the measuring cylinder. The following formula was used to get the bulk density:
Bulk density = Weight of the sample/ Volume of the sample

Tapped density
The volume of a sample's pores and voids is not included in the tapped value, also known as absolute density. Precisely, measured amounts of powders (M) were added to cylinder for measuring. After that, the cylinders were permitted to tap on a bulk density device 100 times. After measuring the height of the tapped powders (V), the following formula was used to get the tapped density:
Tapped density = Weight of the sample/ Volume of the sample

Carr's index and Hausner's ratio
The Carr's index and the Hausner's ratio were determined by measuring both the bulk density and tapped density of the powder. The Carr's and Hausner's ratio were calculated as follows [18]
Carr's index = Tapped density - Bulk density x 100
Bulk density

Solubility study
Domperidone's solubility in several solvents was determined. The excess drug was taken and shaken in a continuous shaker electric bath for 24 hours, dissolved in 20 millilitres of distilled water and other solvents. The solutions were passed through filter paper with a 0.45µ size. 100 ml of this solution were made by diluting 1 ml of it with the same solvent. Using a UV spectrophotometer, the amount of drug (s) dissolved was ascertained; the results are displayed in a table.[19]

Table 2: Solubility of domperidone in different media

S. No.	Solvents	Amount of drug dissolved
1	Water	0.009 ± 0.19 mg/ml
2	0.1 N HCl pH 1.2	0.03± 0.11 mg/ml
3	Phosphate buffer 6.8	0.04 ± 0.15 mg/ml

Preparation of solid dispersion
Two distinct techniques were used for preparing the solid dispersions: the solvent evaporation method and kneading technique with two polymers—modified locust bean gum and modified ziziphus sphina in order to study the effect of individual method or polymer on the final formulation.[20]

Solvent evaporation method:
Solid dispersion was prepared by solvent evaporation method to enhance the solubility of domperidone. The solid dispersion was prepared with, Modified ziziphus sphina Christi gum, and modified locust bean gum the increasing ratios (1:1,1:2,1:3,1:4) by common solvent evaporation method A precise amount of polymer and Domperidone were dissolved in 10 millilitres of ethanol, a typical solvent. To create a homogeneous, transparent solution, the mixture was then agitated for 30 minutes at 100 rpm using a Remi magnetic stirrer. The resulting dispersion's ethanol was then allowed to evaporate overnight on a glass plate containing the clear solution. The various polymer concentrations' amorphous solid dispersions were scraped off and gathered individually. Domperidone amorphous solid dispersions till further examination were tagged and stored out of the reach of light and moisture in the sealed glass vials. [21]

Kneading Method:
Drug was mixed with Modified ziziphus sphina Christi gum and modified locust bean gum in the ratios of 1:1 to 1:4. was wetted with water and kneaded thoroughly for 30 min in a glass mortar. The paste formed was dried under vacuum for 24 h. The dried powder was passed through #60.[22]

Solubility Studies
The solubility study of various Solid dispersions batches was determined in phosphate buffer pH 6.8. A weighed amount of solid dispersion equivalent to drug dose was added in an excess quantity of solvent in screw-capped glass vials. The vials were continuously shaken for 2 h. Finally, the solutions were filtered and analyzed spectrophotometrically at 284nm and it was found that batch SD12 batch have more solubility than other batches.[23]

Table 3: Solubility data of solid dispersion batches

Carrier	Drug carrier ratio	Formulation Code	Technique used	Solubility (mg/ml)
UMZG	1:1	SD1	Solvent evaporation	0.13 ± 0.06
UMZG	1:2	SD2	Solvent evaporation	0.17 ±0.009
UMZG	1:3	SD3	Solvent evaporation	0.21 ± 0.04
MZG	1:1	SD4	Solvent evaporation	0.45± 0.07
MZG	1:2	SD5	Solvent evaporation	0.49 ± 0.41
MZG	1:3	SD6	Solvent evaporation	0.56 ± 0.02
UMZG	1:1	SD7	Kneading method	0.16±0.06
UMZG	1:2	SD8	Kneading method	0.19±0.02
UMZG	1:3	SD9	Kneading method	0.23±0.01
MZG	1:1	SD10	Kneading method	0.29±0.05
MZG	1:2	SD11	Kneading method	0.33±0.08
MZG	1:3	SD12	Kneading method	0.36±0.03

Experimental design

Experiment design is the process of planning, carrying out, and analysing test findings through a limited number of experiments. Separate factors if by chance varied, scientists demonstrate their understanding of a subject by producing their product or process via experimental design.

Using Design-Expert software version 12, Box-Behnken Design was utilised to prepare fast dissolving Domperidone tablets.

The independent variables selected were croscarmellose, sodium starch glycolate and crospovidone. The response variables studied were hardness, in- vitro dissolution and disintegration time. With the emergence of user-friendly tools, design ideas such as Design of Experiments (DoE) are used to complete the design space tools as well as the legal requirements are recommended.[24]

It is hard to identify the elements that impacted the outcome if there are several independent variables that fluctuate randomly. Although the characteristics differ to a fair extent, the DoE expects simple approaches. A DoE application can serve a variety of functions.

research to determine the key variables influencing the process or product under study; whole or in part designs for quantifying factorial outcomes; comprehensive response studies, which are especially useful for optimisation; mixed designs, etc.

To ensure that the product stays within the specification, robustness is used as a last test prior to product release, and optimisation is used to obtain a combination of parameters connected to the response. Any experimental study's main objective is to determine the relationship between independent variables, or factors, and dependent variables, or outcomes, or results, within the experimental structure. variables like the quantity of ingredients, the characteristics of the materials, the independent variable during processing, the dependent variables, etc. are characteristics or attributes of the product that show the consistent execution of the procedure. [25] Generally, the test (experimental) design is employed to concurrently examine the impacts of several independent variables (factors) on response variability; as a result, it is a technique for multivariate analysis.[26]

Formulation of Optimized Fast Disintegrating Tablet:

Tablets were formulated by multi tooling lab scale punching machine (Karnavati) at slow speed and high compression pressure to avoid capping. The dry blend was compressed into tablets using an 8 mm circular punch. The fabricated tablets from all the batches were then separately evaluated for post-compression studies like their organoleptic characteristics, size, shape, thickness, diameter, hardness, friability, wetting time and wetting volume, water adsorption ratio, weight variation test, contentof active ingredient, uniformity of dispersion, In- vitro dispersion time, In- vitro disintegration time, In-vitro dissolution studies, and stability studies.

Table 4: Box Behnken design with 3 factors and 15 runs

Formulation Code	Crospovidone (mg)	Sodium Starch Glycolate(mg)	Croscarmellose (mg)
F1	19.5	18	9

F2	15	15	15
F3	24	12	12
F4	19.5	12	9
F5	15	15	9
F6	15	12	12
F7	19.5	15	12
F8	19.5	15	12
F9	24	18	12
F10	24	15	9
F11	24	15	15
F12	19.5	18	15
F13	19.5	15	12
F14	19.5	12	15
F15	15	18	12

Results and Discussion

Table 5: Characterization of tablet blends

Formulation Code	Bulk Density	Tapped Density	Hausner's Ratio	Compressibility Index	Angle of Repose
F1	0.731 ±0.012	0.395 ±0.013	1.071 ±0.012	6.604 ±1.330	23.34 ±1.363
F2	0.408 ±0.145	0.436 ±0.012	1.065 ±0.024	5.621 ±1.233	25.19 ±1.221
F3	0.383 ±0.023	0.405 ±0.021	1.048 ±0.013	4.556 ±1.422	27.35 ±1.007
F4	0.387 ±0.004	0.421 ±0.002	1.059 ±0.015	5.623 ±1.221	24.44 ±1.126
F5	0.406 ±0.013	0.427 ±0.005	1.073 ±0.010	6.792 ±1.012	25.99 ±1.096
F6	0.403 ±0.025	0.433 ±0.006	1.065 ±0.003	6.076 ±1.231	23.56 ±1.132
F7	0.409 ±0.034	0.436 ±0.014	1.069 ±0.006	6.422 ±1.086	26.59 ±1.165
F8	0.384 ±0.006	0.405 ±0.017	1.057 ±0.016	5.432 ±1.097	26.32 ±1.136
F9	0.396 ±0.017	0.424 ±0.023	1.082 ±0.027	7.601 ±1.242	25.22 ±1.432
F10	0.405 ±0.005	0.429 ±0.023	1.095 ±0.010	8.756 ±1.134	23.59 ±1.243
F11	0.399 ±0.018	0.417±0.012	1.059±0.015	5.594±1.123	25.62±0.096
F12	0.402 ±0.017	0.422 ±0.007	1.067 ±0.023	6.294 ±1.324	23.54 ±0.847
F13	0.381 ±0.009	0.435 ±0.013	1.051 ±0.012	6.504 ±1.220	24.24 ±1.361
F14	0.384 ±0.013	0.406 ±0.012	1.072 ±0.024	5.250 ±1.022	25.19 ±1.201
F15	0.372 ±0.005	0.396 ±0.011	1.060 ±0.016	6.204 ±1.422	27.35 ±1.007

Solubility Studies

The solubility study of various Solid dispersions batches was determined in phosphate buffer pH 6.8. A weighed amount of solid dispersion equivalent to drug dose was added in an excess quantity of solvent in screw-capped glass vials. The vials were continuously shaken for 2 h. Finally, the solutions were filtered and analyzed spectrophotometrically at 284nm and it was found that batch SD12 batch have more solubility than other batches.[23]

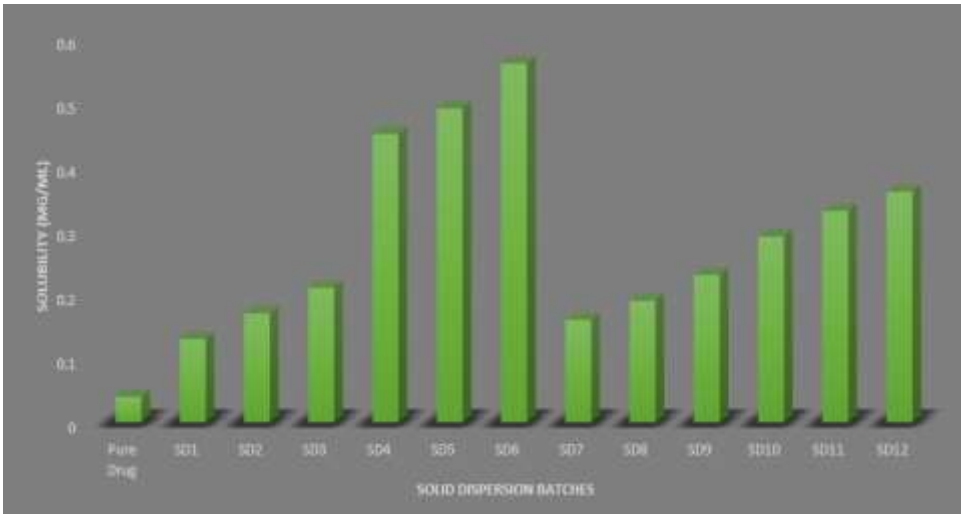

Fig. 3: Solubility of solid dispersion prepared by solvent evaporation and kneading method in 6.8 phosphate buffer

Analysis of Data by Design Expert Software

The analysis of variance (ANOVA) and multiple regression analyses were done using Stat-Ease Design Expert 12 software. The statistical treatment and interpretation of data were essential steps where the p-value indicated main effects on optimization of the formulation. ANOVA (Analysis of Variance) is a statistical method used to determine if there are significant differences between the means of three or more groups. When using Design Expert Software for ANOVA, the software facilitates the design and analysis of experiments, particularly in determining the effect of multiple factors on a response variable. [27]

ANOVA for Linear model

Table 6: Response 1: Hardness

Source	Sum of square	df	Mean Square	F-value	p-value	
Model	0.5398	3	0.1799	21.77	< 0.0001	Significant
A-Crospovidone	0.4095	1	0.4095	49.55	< 0.0001	
B-Sodium starch glycolate	0.0990	1	0.0990	11.98	0.0042	
C-Croscarmellose sodium	0.0313	1	0.0313	3.78	0.0738	
Residual	0.1074	13	0.0105			
Lack of fit	0.0942	9	0.0033	3.115	0.1405	not significant
Pure error	0.0133	4				
Cor Total	0.6472	16				

The Model F-value of 1.69 implies the model is not significant relative to the noise. There is a 24.05% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case AB is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Table 7: Response 2: In vitro dissolution (%)

Source	Sum of square	df	Mean Square	F-value	p-value	
Model	211.45	3	70.48	78.37	< 0.0001	Significant
A-Crospovidone	146.63	1	146.63	163.04	< 0.0001	
B-Sodium starch glycolate	63.85	1	63.85	70.99	0.0042	
C-Croscarmellose sodium	0.9730	1	0.9730	1.08	0.0738	
Residual	11.69	13	0.8993			
Lack of fit	8.69	9	0.9650	1.28	0.1405	not significant
Pure error	3.01	4	0.7516			
Cor Total	223.14	16				

Table 8: Response 3: In vitro disintegration time

Source	Sum of square	df	Mean Square	F-value	p-value	
Model	189.7	3	63.19	34.10	< 0.0001	Significant
A-Crospovidone	182.40	1	182.40	98.43	< 0.0001	
B-Sodium starch glycolate	0.3200	1	0.3200	0.1727	0.6845	
C-Croscarmellose sodium	6.84	1	6.84	3.69	0.0768	
Residual	24.09	13	1.85			

Lack of fit	20.46	9	2.27	2.51	0.1951	not significant
Pure error	3.63	4	0.9070			
Cor Total	213.66	16				

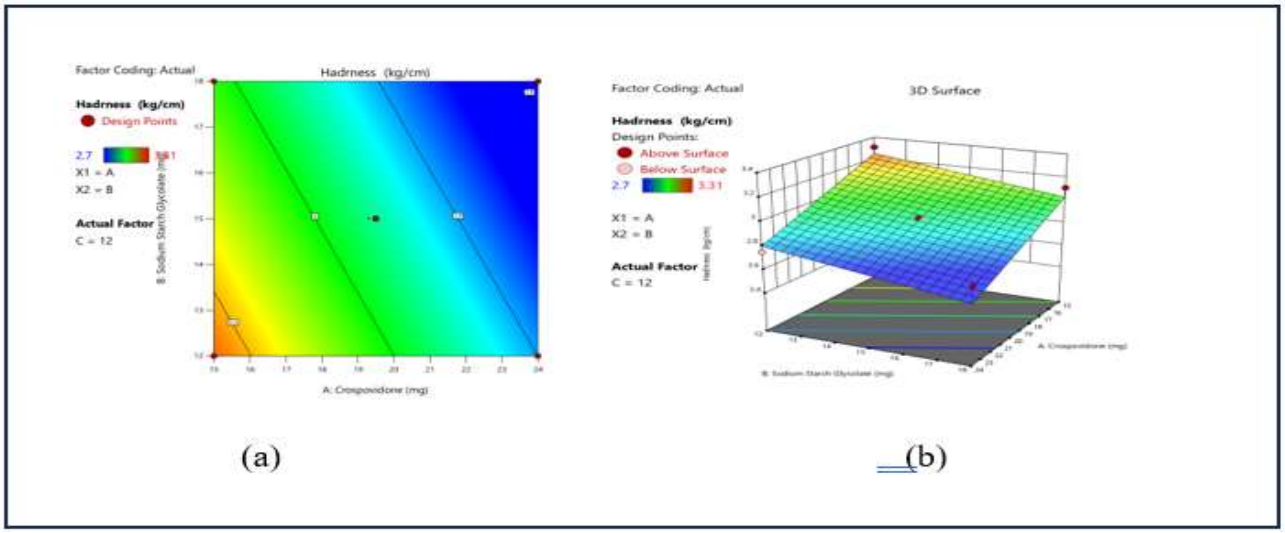

Fig. 4: Contour plot and 3D surface plot showing the effect of Crospovidone and Sodium starch glycolate on hardness of tablet

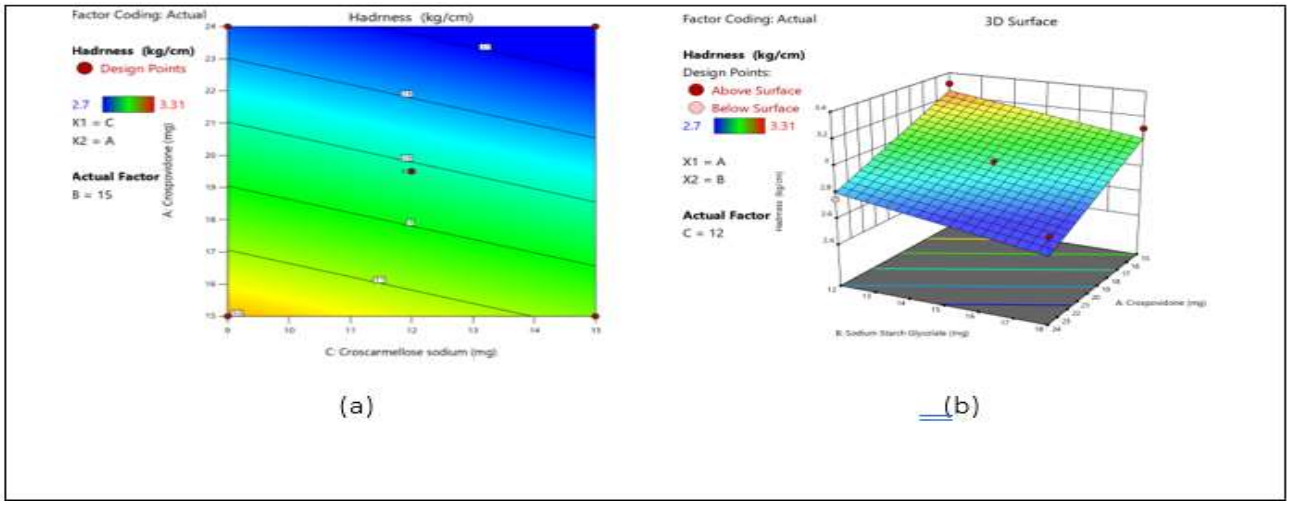

Fig. 5: (a) Contour and (b)3D surface plot showing the effect of croscarmellose sodium and crospovidone on the hardness of tablet

Contour plot and 3d surface plot showing that as the concentration of crospovidone increases the hardness of the tablet decreases whereas sodium starch glycolate showing the little bit effect on the hardness of tablet whereas croscarmellose has no or little effect on the hardness of the tablet.

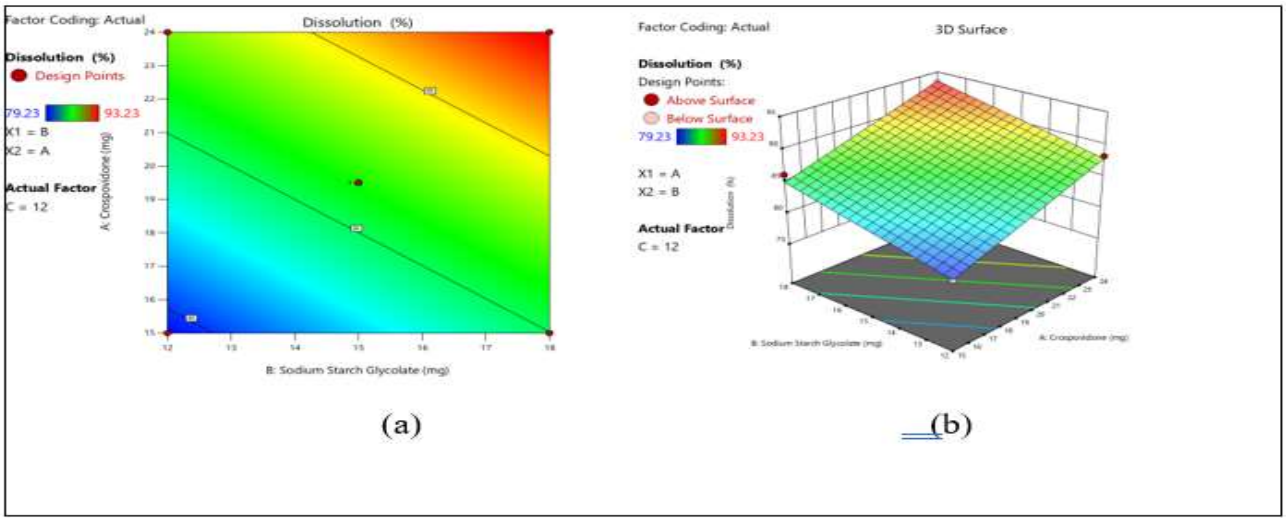

Fig. 6: Contour plot and 3D surface plot showing the effect of Crospovidone and Sodium starch glycolate on the dissolution percentage of tablets.

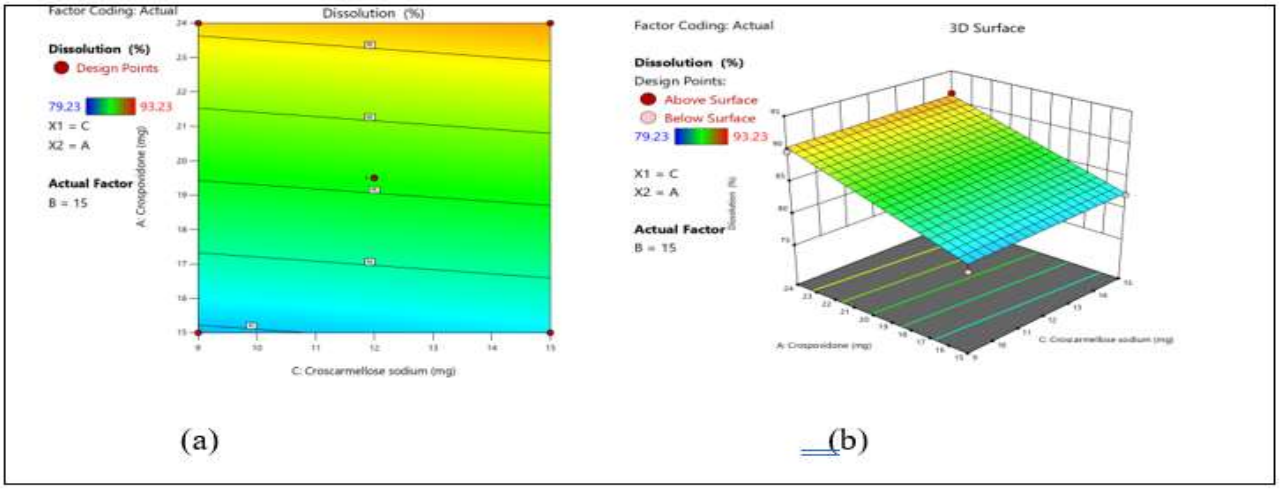

Fig. 7: Contour plot and 3D surface plot showing the effect of Crospovidone and Croscarmellose sodium on the dissolution percentage of tablets.

Contour plot and 3d surface plot showing that as the concentration of crospovidone increases the cumulative drug release of drug increases after 12 minutes. Sodium starch glycolate also showing the increase in the cumulative drug release as the concentration increases, whereas croscarmellose sodium showing no effect on the cumulative drug release as the concentration increases or decreases.

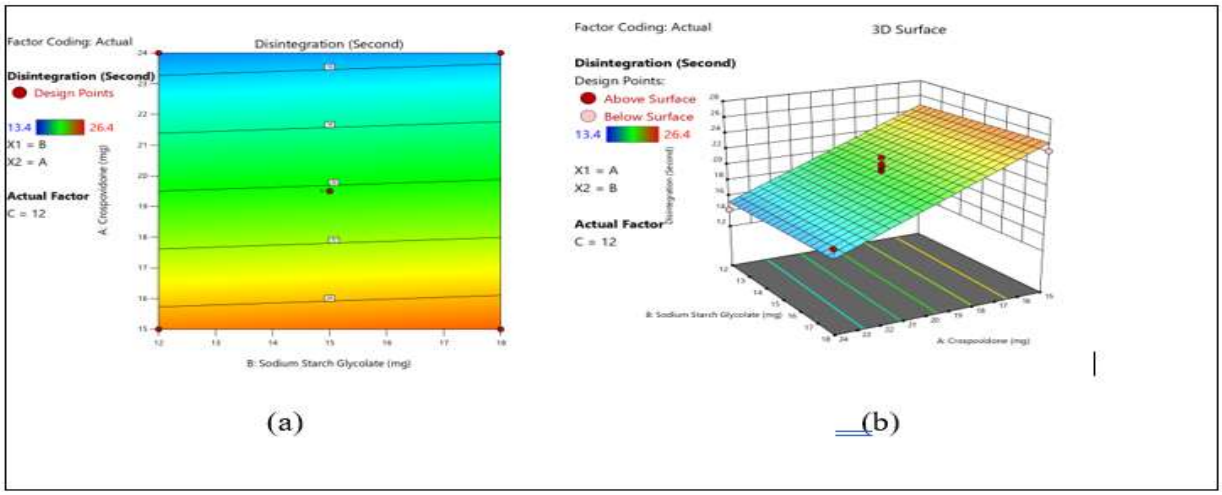

Fig. 8 Contour plot and 3D surface plot showing the effect of Crospovidone and Sodium starch glycolate on the disintegration time of Tablets.

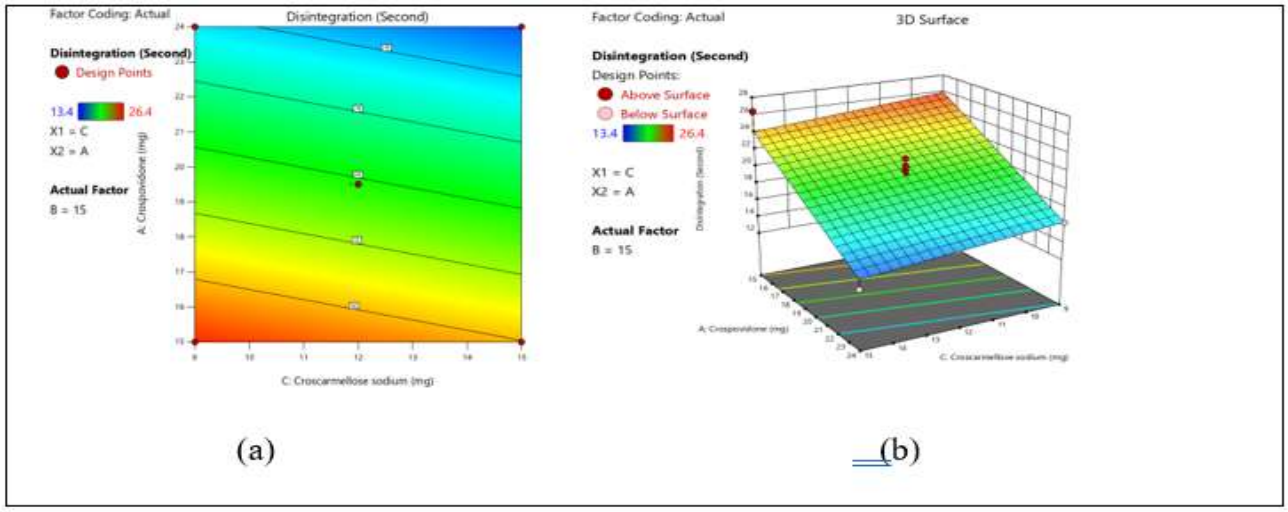

Fig. 9: Contour plot and 3D surface plot showing the effect of Crospovidone and croscarmellose sodium on the disintegration time of tablets.

Concentration of croscarmellose not showing any effect in disintegration time of drug, whereas there was a slightly decrease in the disintegration time of tablet as the concentration of sodium starch glycolate increases.

In-Vitro dissolution study

In-vitro dissolution studies were successfully carried out for all formulations of Fast dissolving tablets. Paddle type dissolution apparatus was used to carry out in-vitro drug release studies. 900 ml of phosphate buffer pH 6.8, maintained at 37±0.5ºC, was filled in each basket and then dropped one tablet in each. 2 ml of samples were withdrawn separately from each batch at uniform intervalsof 2 minutes for 12 minutes. 2ml of fresh dissolution medium was replaced after each time of withdrawal of the sample. The samples were filtered, diluted, and then were analyzed spectrophotometrically at 284 nm for the drug release against the respective water blank.

The dissolution study for all formulations was carried out until a constant drug releasevalue was obtained which was indicative of the maximum drug release limit at some time that is possible from that particular formulation and that no further amount of drugwill be released after that point no matter how long the dissolution is carried out. It was observed for all the formulations that maximum drug release took place in 12 minutes and therefore the study was not carried out for more than 12 minutes.

Table 3: In-vitro dissolution data of formulations (F1-F15)

	Percentage of Drug Release at various time points					
Formulation code	**Time (Min)**					
	2	**4**	**6**	**8**	**10**	**12**
F1	24.38 ± 0.14	38.23±0.2	54.68±1.2	73.15±0.8	84.68±0.2	90.3 ±1.21
F2	21.23 ± 0.18	44.68±1.3	58.23±0.6	68.3 ±0.43	75.28±2.1	82.7 ±0.67
F3	26.28 ± 1.23	40.19±0.3	53.82±0.2	69.6 ±1.35	76.28±0.4	88.8 ±0.14
F4	22.38 ± 0.09	43.28±0.3	60.2±0.30	69.28±0.8	78.8±1.11	84.28±0.07
F5	21.32 ± 0.25	39.38±1.1	60.1 ±0.19	69.23±1.3	4.32±0.35	80.32±0.9
F6	20.81 ± 0.31	39.28±0.4	59.31±1.3	70.28±1.6	77.26±1.1	86.26±1.2
F7	27.54 ± 0.29	46.23±0.3	60.2 ±1.11	68.32±0.4	77.23±1.2	86.83±0.05
F8	24.23 ± 1.19	41.23±0.39	64.82±1.8	76.38 ± 1.4	80.28±0.69	86.35 ±0.76
F9	31.32 ± 0.64	51.19±0.70	69.18±0.4	76.28±0.78	85.21±0.18	91.23±0.09

F10	29.12 ± 0.10	46.28±1.48	60.32±1.7	71.17 ± .17	80.12±0.41	89.12±0.07
F11	31.28 ± 1.18	52.28±0.39	71.8 ±0.72	82.21 ±1.8	88.41±1.53	90.36 ±0.11
F12	27.23 ± 1.29	51.18±1.30	65.37±1.2	77.18±1.58	82.21±0.51	89.47 ±0.48
F13	28.63 ± 1.13	51.29±0.19	68.61±0.3	79.12±0.17	82.21±1.16	86.36 ±0.76
F14	23.36 ± 1.53	41.11±0.32	62.19±0.6	74.88±0.69	80.19±1.21	84.69 ±0.87
F15	28.29 ± 0.17	46.51±0.16	67.29±1.8	74.28±1.18	80.29±0.27	86.14±0.006
F16	34.25± 0.14	54.48±0.11	69.25±1.1	78.36±0.21	86.32±1.25	93.64±0.14

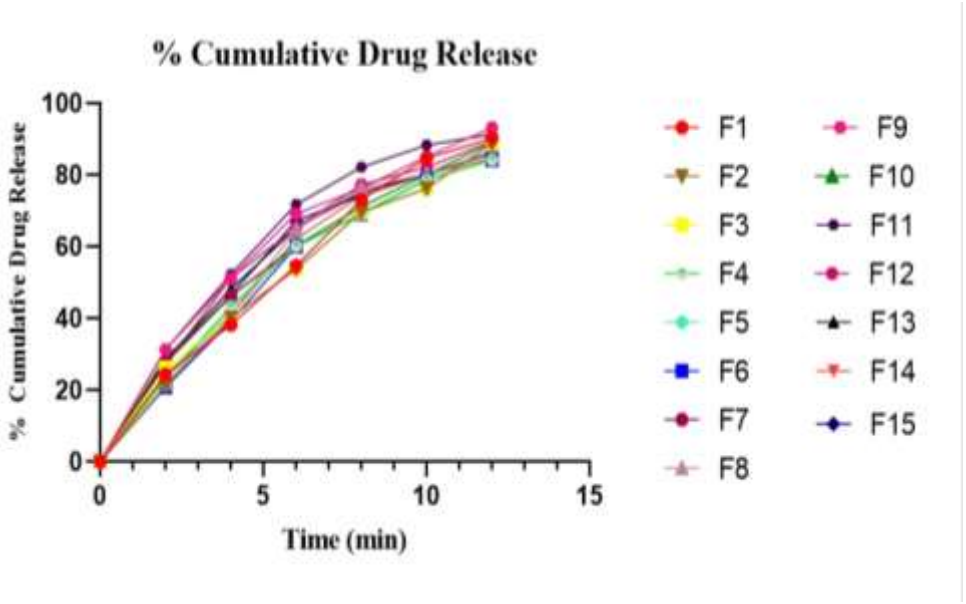

Fig. 10: In-vitro drug release of Domperidone formulations(F1-F15)

Stability studies:
The stability studies were carried out on the most satisfactory formulations as per ICH guideline Q1C. The most satisfactory formulation was filled in high-density polyethylene bottle which is sealed with aluminum packaging and kept in the humidity chamber maintained 40 ± 2°C/75% ± 5% relative humidity (RH) for 1 month. At the end of studies, samples were analyzed for the assay and *in vitro* drug release. Solid state property of solid dispersion after stability period was also characterized by DSC.

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Conclusion
In conclusion, this study explored the potential of natural carriers for improving the solubility of fast dissolving tablets (FDTs). The results demonstrated that incorporating natural carriers successfully enhanced the drug's solubility, leading to faster dissolution rates compared to the control formulation. This approach offers a safe and potentially more consumer-friendly alternative to synthetic excipients for FDT development. Further research is warranted to optimize the formulation process and explore the long-term stability of these natural carrier-based FDTs. Additionally, in vivo studies could be conducted to confirm the bioavailability improvements achieved through this method. Overall, this research paves the way for the development of more effective and patient-centric FDTs utilizing natural resources.

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