International Journal of Pharmacology and Clinical Research (IJPCR)

IJPCR |Vol.8 | Issue 1 | Jan - Mar -2024

www.ijpcr.com

DOI : https://doi.org/10.61096/ijpcr.v8.iss1.2024.28-35

ISSN: 2349-5448

Research

Development, characterization of solid dispersion of irinotecan by solvent evaporation method

Paramkoosham Sai Lakshmi[1*], D.Venkata Ramana, K. Sai Kiran, J. Pravalika

[1]*Department of Pharmaceutics, Holy Mary Institute of Technology & Science (College of Pharmacy), Bogaram Village, Keesara Mandal, Hyderabad, Telangana, India*

[*]Author for Correspondence: Paramkoosham Sai Lakshmi
Email: sailakshmi3377@gmai.com

Published on: 07 Feb 2024

Published by:
DrSriram Publications

Abstract

The present study was carried out on Irinotecan by employing solid dispersion technique. The λ_{max} of phosphate buffer pH 6.8 of Irinotecan were found to be at 247nm. The pure drug the optimised Solid dispersion formulations were subjected to FTIR studies. The results were showed that there is no interaction between the drug and excipients. The micrometric properties of blend of Irinotecan soild dispersion were characterized with respect to Angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio**.** Angle of repose was less than 28^0, Carr's index values were 10 to 17 for the pre compression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.2 for all the batches indicating good flow properties. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 2 to 3 kg/cm^2 and the friability values were less than 1% indicating that the tablets were compact and hard. The thickness of the tablets ranged between 3.1 to 3.8 mm. All the formulations satisfied the content of the drug as they contained 96-100% of Irinotecan and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control limits. The dissolution profile of Irinotecan tablets were compared between solid dispersion tablets. The Irinotecan solid dispersion tablets showed better release in phosphate buffer pH 6.8, in that F2 showed good drug release i.e., 99.89 at 15 minutes. F2 formulation was taken as optimised formulation.

Keywords: Irinotecan, solid dispersion tablets

INTRODUCTION

From the last few years, the pharmaceutical scientists were working to develop patient compliance and safe dosage forms due to enhanced demand in the market for them. As a result developing the new technologies has been increasing annually because the development of new drug molecule requires high cost rather than new technology. So the current trend in most of pharmaceutical industries is development of dosage form with new formulation technology using old drug molecules to improve safety, efficacy and patient compliance.[1]

Oral drug delivery is still preferred way of administration for most of the active drug molecules due to its several advantages were greater flexibility in design and high patient compliance. Because of greater stability, accuracy in dose, easy of production, formulation of tablets is preferred oral dosage form. But the poor dissolution of water insoluble drugs is the major problem for pharmaceutical formulators to prepare in the form of tablets. The absorption rate of a poorly water-soluble drug, formulated as an orally administered solid dosage form, is controlled by its dissolution rate in the fluid at the absorption site. The dissolution rate is often the rate-determining step in drug absorption. Since they exhibit poor and erratic dissolution profiles, most water-insoluble drugs are included by the FDA in the list of drugs having a high risk for therapeutic in equivalence due to differences and inconsistencies in bioavailability. Therefore, the solubility and dissolution behavior of a drug are the key determinants of the oral bioavailability.[2]

The term "water-insoluble drugs" includes those drugs that are "sparingly water-soluble" (1 part solute into 30 to 100 parts of water), "slightly water-soluble" (1 part solute into 100 to 1000 parts of water), "very slightly water-soluble" (1 part solute into 1000 to 10,000 parts of water), and "practically water-insoluble" or "insoluble" (1 part solute into 10,000 or more parts of water) [3].

Compounds with poor aqueous solubility are increasingly posing challenges in the development of new drugs, since a large number of drugs coming directly from synthesis or from high throughputs screenings have a poor solubility[4]. The ability to increase aqueous solubility is thus a valuable aid to increase the efficacy for poorly water soluble drugs.

Biopharmaceutical classification system

A Biopharmaceutics Classification System (BCS) was introduced by Amidon et al[6] as a basis for predicting the likelihood of *in vitro-in vivo* correlations for immediate release dosage forms, based on the recognition that drug solubility/dissolution properties and gastrointestinal permeability are the fundamental parameters controlling the rate and extent of drug absorption.[4]

The BCS was developed primarily in the context of immediate release solid oral dosage forms. It is the scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. It is the drug development tool that allows estimation of the contributions of three major factors, dissolution, solubility and intestinal permeability that affect oral drug absorption from immediate release solid oral dosage forms. It was first introduced into regulatory decision making process into guidance document of immediate release solid oral dosage forms: scale up and post approval changes.[5]

The Biopharmaceutical classification system classifies into four groups according to their solubility and permeability. The basis for this classification is the under standing that drug dissolution from the dosage form depends considerably on its solubility and that absorption from the gastrointestinal dependant on permeability properties of the drug substances.[6]

Class I: High Solubility - High Permeability,
Class II: Low Solubility - High Permeability,
Class III: High Solubility - Low Permeability and
Class IV: Low Solubility - Low Permeability.

Class I compounds are typical examples for waiving bioequivalence studies. In the selection process, new chemical compounds with a low aqueous solubility and low permeability are preferably filtered out since they might pose problems during pharmaceutical development. The rate limiting step for drug absorption is drug dissolution or gastric emptying if dissolution is very rapid.[7] *In vitro in vivo* correlation is expected if dissolution rate is slower than gastric emptying time. E.g., Propronolol, Metoprolol, Diltiazem, Verapamil.

Class II drugs have a high absorption number but a low dissolution number. As these drugs exhibit low solubility, dissolution or release from the dosage form occurs slowly and the dissolution rate will become the rate-limiting factor for drug absorption. These drugs exhibit varying bioavailability and need enhancement in dissolution rate for increasing bioavailability.[8] *In vitro in vivo* correlation is usually expected for class II drugs.
E.g., Ketoconazole, Mefenamic acid, Nisoldipine, Nifedipine

It is evident that for class II drugs the low ability to dissolve is a more important limitation to their overall rate and extent of absorption than their ability to permeate through the intestinal epithelia. There are several pharmaceutical strategies Drug micronization, solid dispersion, co precipitation, lyophilization, micro encapsulation and inclusion of drug solutions or liquid drugs into soft gelatin capsules or specially sealed hard shell capsules are some of the major formulation tools which have been shown to enhance the dissolution characteristics of water-insoluble drugs.[9]

For Class III drugs, permeation through the intestinal membrane forms the rate-limiting step. Bioavailability is independent of drug release from the dosage form. Limited or no *In vitro in vivo* correlation with dissolution rate is observed.[10] E.g., Acyclovir, Neomycin B, Captopril, Enalaprilate.

Class IV drugs exhibit poor and variable bioavailability. Several factors such as dissolution rate, permeability, gastric emptying form the rate-limiting steps for absorption of these drugs. No correlation or limited *In vitro in vivo* correlation is expected.[11] E.g., Chlorthiazide, Furosemide.

MATERIALS AND METHODS

Irinotecan Procured from CIPLA Pharma, Provided by Sura Labs, PEG 4000 from Nihar traders pvt Ltd, Polaxomer from Nihar traders pvt Ltd, Camphor from Nihar traders pvt Ltd, Magnesium stearate from Himedia Laboratories, SSG from Nice chemicals Ltd, Mannitol from Nihar traders pvt Ltd, Talc from S.D. Fine chemical Pvt.Ltd, Mumbai, Explotab from Himedia Laboratories, Polyplasdone XL from Finar chemicals Ltd.

Analytical method development

Determination of Wavelength

10 mg of pure drug was dissolved in 10 ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

Determination of Calibration Curve

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution required concentrations were prepared (shown in Table) and those concentrations absorbance were found out at required wavelength.

Fourier Transform Infrared (FTIR) spectroscopy

The formulations were subjected to FTIR studies to find out the possible interaction between the drug and the excipients during the time of preparation. FT IR analysis of the Pure drug and optimised formulation were carried out using an FT IR spectrophotometer (Bruker FT-IR - GERMANY).

Formulation Development

Formulation development for solid dispersion

Solid dispersions were prepared by solvent evaporation method. Methanol was used as solvent. Irinotecan and Water soluble polymers such as Polaxomer and PEG 4000 were selected as carriers. Drug and polymers were taken in 1:1 ratio stated in the formulation chart (Table). The prepared solid dispersions were passed through the sieve no 20 to get uniform sized particles. The solid dipersions were mixed with required quantities of super disintegrants, diluent, lubricant and glidant . The blend was evaluated for precompression parameters.

Table 1: Formulation of solid dispersion showing various compositions (Ratios only)

	SD1	SD2	SD3	SD4	SD5
Drug	1	1	1	1	1
Polaxomer	1	2	--	--	1
PEG 4000	--	--	1	2	1

Table 2: Formulation of tablet by using solid dispersion

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Equivalent to 10mg	SD1 (40m)	SD1 (40mg)	SD1 (40mg)	SD1 (40mg)	SD1 (40mg)	SD1 (40mg)	SD1 (40mg)	SD1 (40mg)	SD1 (40mg)	SD1 (40mg)
Explotab/sodium starch glycolate	20	20	20	20	20	-	-	-	-	-
Crosspovidone	-	-	-	-	-	15	15	15	15	15
Mg.stearate	5	5	5	5	5	5	5	5	5	5
Aerosil	5	5	5	5	5	5	5	5	5	5
Mannitol	80	80	80	80	80	85	85	85	85	85
Total weight	150	150	150	150	150	150	150	150	150	150

RESULTS & DISCUSSION

Analytical Method Development

Construction of calibration curve for Irinotecan

The λmax of phosphate buffer pH 6.8 of Irinotecan were found to be at 247 nm. Standard graphs of Irinotecan in phosphate buffer pH 6.8 were shown in Table 7.1. Good linearity was observed with concentration verses absorbance. Its R^2 value in 0.1N HCl and phosphate buffer pH 6.8 was0.999 which were very nearer to '1' and so obeys "Beer -Lambert" law.

Table 3: Calibration curve of Irinotecan in phosphate buffer pH 6.8

Concentration(µg/mL)	Absorbance
0	0
5	0.145
10	0.309
15	0.439
20	0.585
25	0.747

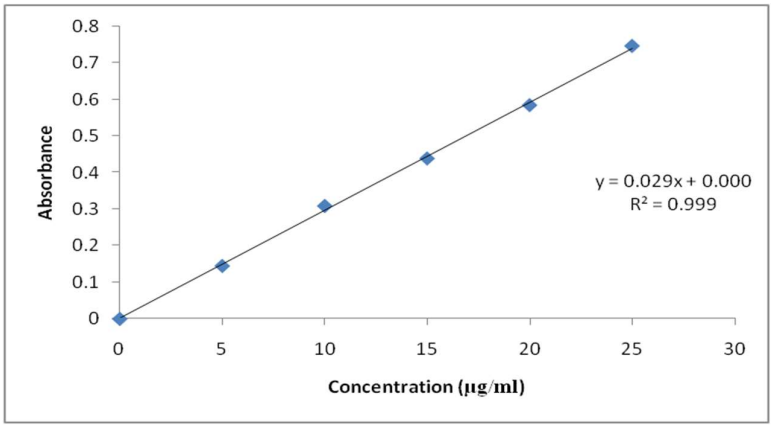

Fig 1: Calibration curve of Irinotecan in phosphate buffer pH 6.8

Drug Excipient Interactions

Fourier transform infrared (FTIR) spectroscopy studies

The pure drug and the optimised formulation (F2) were subjected to FTIR studies. The results were showed that there is no interaction between the drug and excipients.

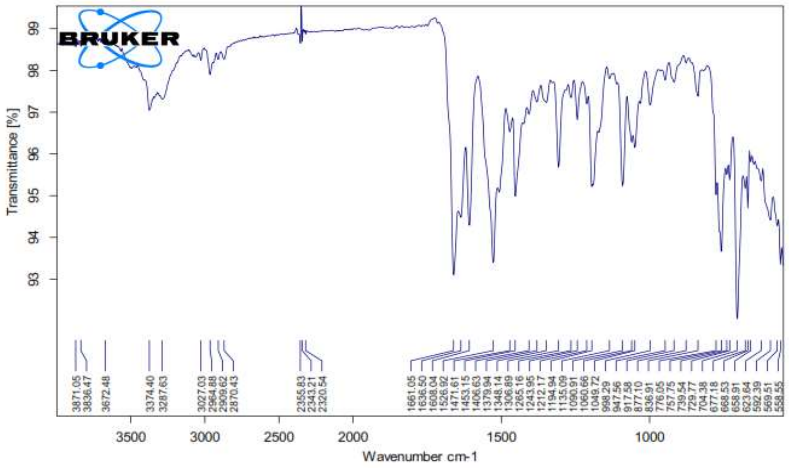

Fig 2: FT-IR Spectrum of Irinotecan pure drug.

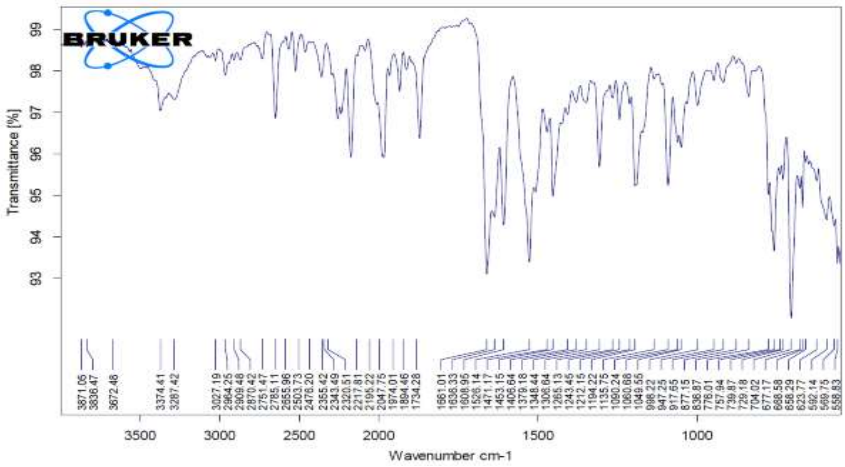

Fig 3: FT-IR Spectrum of Optimised Formulation (F2)

Post compression parameters

The results of the weight variation, hardness, thickness, friability, and drug content of the solid dispersion tablets were given in Table. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 2 to 3 kg/cm^2 and the friability values were less than 1% indicating that the tablets were compact and hard. The thickness of the tablets ranged between 3.1 to 3.8 mm. All the formulations satisfied the content of the drug as they contained 96-100% of Irinotecan and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control limits.

Table 4: Evaluation of post compression parameters of solid dispersion tablets

Formulation code	Average Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%loss)	Disintegration time (sec)	Content uniformity (%)
F1	98	3.2	2.5	0.39	18	96.31
F2	99	3.1	2.1	0.29	14	98.34
F3	101	3.4	2.7	0.32	17	97.36
F4	99.8	3.6	2.4	0.41	16	96.42
F5	102	3.8	2.6	0.26	18	96.59
F6	101	3.3	2.7	0.28	19	99.33
F7	100	3.5	2.2	0.37	20	99.45
F8	102	3.2	2.3	0.48	22	99.56
F9	101	3.2	2.8	0.54	24	98.96
F10	101	3.4	2.2	0.65	23	98.78

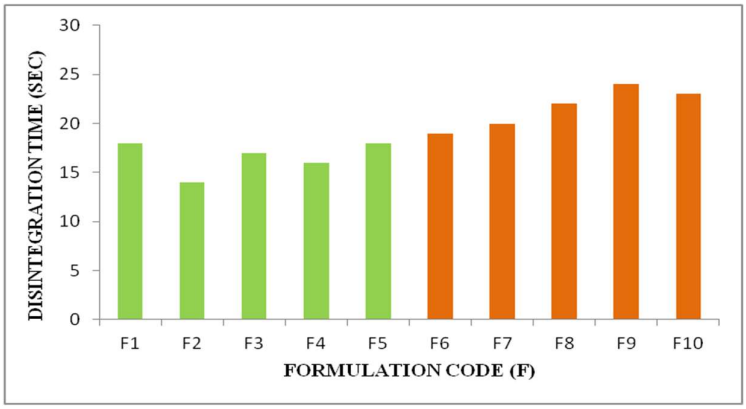

Fig 4: Pre and post compression of solid dispersion tablets

From the above pre and post compression of solid dispersion tablets of all the required evaluation tests were found to be within limit. Less disintegration time is F2 formulation i.e., 14 seconds.

***In vitro* Dissolution Studies**

All the solid dispersion formulations of Irinotecan were subjected to *In vitro* dissolution studies, these studies were carried out using phosphate buffer pH 6.8 by using dissolution apparatus type II.

The dissolution profile of Irinotecan tablets were compared between solid dispersion tablets. The Irinotecan solid dispersion tablets showed better release in phosphate buffer pH 6, in that F2 showed good drug release i.e., 99.89 at 15 minutes.

Table 5: *In vitro* dissolution studies of formulated solid dispersion tablets by using Explotab/sodium starch glycolate as super disintegrant

Time(min)	F1	F2	F3	F4	F5
0	0	0	0	0	0
5	29.86	36.33	21.5	30.48	31.06
10	42.72	62.18	56.8	53.61	59.88
15	68.75	99.89	58.75	69.83	79.52
20	80.35		70.35	82.41	95.64
30	87.94		77.94	96.54	
45	96.24		89.5		
60	96.24		91.3		

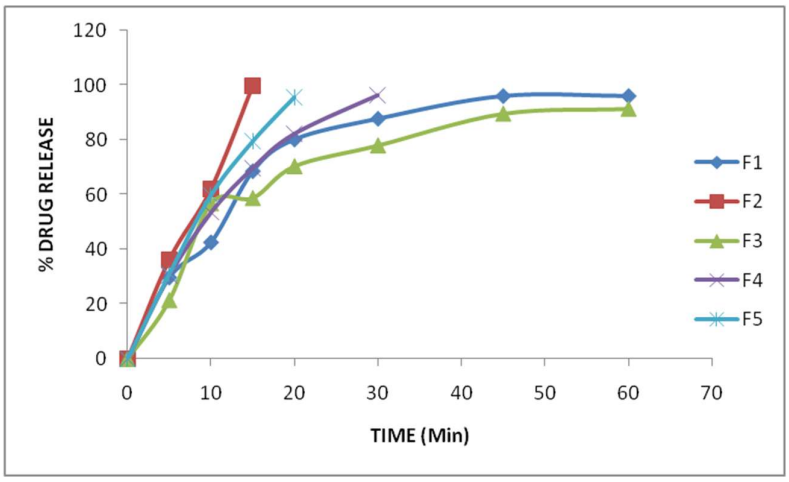

Fig 5: *In vitro* dissolution studies of formulated solid dispersion tablets by using Explotab/sodium starch glycolate as super disintegrant

Table 6: *In vitro* dissolution studies of formulated solid dispersion tablets by using Crosspovidone as super disintegrant

Time(min)	F6	F7	F8	F9	F10
0	0	0	0	0	0
5	32.86	44.33	21.5	30.47	28.96
10	54.56	59.89	32.8	38.48	39.16
15	69.75	88.2	49.75	52.68	58.97
20	73.34	97.2	52.32	69.46	78.65
30	81.94		58.94	82.17	87.53
45	96.5		63.28	96.58	
60	96.5		88.14	96.58	

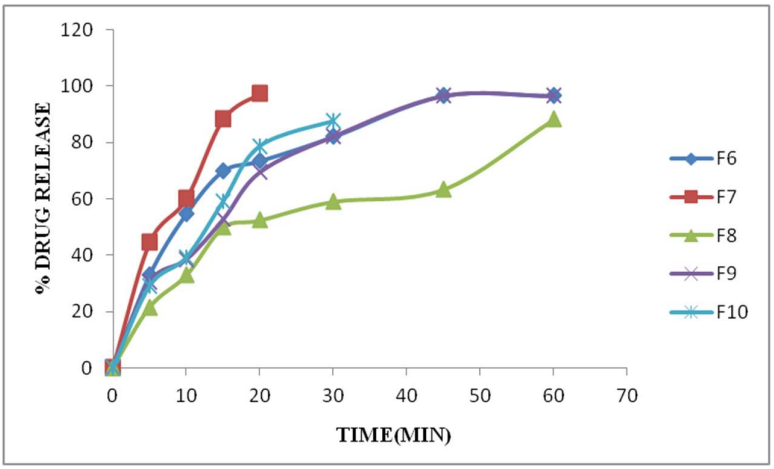

Fig 6: *In vitro* dissolution studies of formulated solid dispersion tablets by using Crosspovidone as super disintegrant

From the above graphs it was revealed that F2 formulation was optimised formulation. Why because in that F2 showed good drug release i.e., 99.89% at 15 minutes. and less disintegration time is F2 formulation i.e., 14 seconds. Hence F2 formulation considered as optimised formulation.

CONCLUSION

The present study was carried out on Irinotecan by employing solid dispersion technique. The λ_{max} of phosphate buffer pH 6.8 of Irinotecan were found to be at 247 nm. Standard graph of Irinotecan in phosphate buffer pH 6.8 was plotted. Good linearity was observed with concentration verses absorbance. Its R^2 value in phosphate buffer pH 6.8 was0.999 which were very nearer to '1' and so obeys "Beer -Lambert" law.

The pure drug the optimized Solid dispersion formulations were subjected to FTIR studies. The results were showed that there is no interaction between the drug and excipients. The micrometric properties of blend of Irinotecan soild dispersion were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio**.** Angle of repose was less than 28^o, Carr's index values were 10 to 17 for the pre compression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.2 for all the batches indicating good flow properties.

The results of the weight variation, hardness, thickness, friability, and drug content of the solid dispersion tablets were given in Table. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 2 to 3 kg/cm^2 and the friability values were less than 1% indicating that the tablets were compact and hard. The thickness of the tablets ranged between 3.1 to 3.8 mm. All the formulations satisfied the content of the drug as they contained 96-100% of Irinotecan and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control limits.

All the solid dispersion formulations of Irinotecan were subjected to *in vitro* dissolution studies, these studies were carried out using phosphate buffer pH 6.8 by using dissolution apparatus type II.

The dissolution profile of Irinotecan tablets were compared between solid dispersion tablets. The Irinotecan solid dispersion tablets showed better release in phosphate buffer pH 6.8, in that F2 showed good drug release i.e., 99.89 at 15 minutes. F2 formulation was taken as optimised formulation.

REFERENCES

1. Chein, Y. W. *Oral Drug Delivery and Delivery Systems*, 2nd ed.; Marcel Dekker, 1992.
2. Kaur T, Gill B, Kumar S, Gupta GD. Mouth dissolving tablets: a novel approach to drug delivery. Int J Curr Pharm Res. 2011;3(1):1-7.
3. Augsburger, L. L.; Stephen, W. H.. Orally disintegrating tablets. Pharmaceutical dosage forms: tablets. Infroma Healthcare Publication, 3rd ed., *2*, 293–312.
4. Schwartz, B. J.; Connor, R. E. *Optimization Technique in Pharmaceutical Formulations and Processing. Modern Pharmaceutics*, 3rd ed.; Marcel Dekker Inc., 1996, pp 607–624.
5. Bolton, S. *Pharmaceutical Statistics- Practical and Clinical Applications*, 3rd ed.; Marcel Dekker Inc., 1997.

6. Two level full factorial tutorials. Design expert Software, Version 8.0.4.1, users guide. Inc., New York.
7. Balter MS, La Forge J, Low DE, Mandell L, Grossman RF, Chronic Bronchitis Working Group. Canadian guidelines for the management of acute exacerbations of chronic bronchitis. Canadian respiratory journal. 2003;10(suppl b):3B-2B. https://www.hindawi.com/journals/crj/2003/486285/abs/
8. Schiermeier S, Schmidt PC. Fast dispersible ibuprofen tablets. European journal of pharmaceutical sciences. 2002 Apr 1;15(3):295-305. https://www.sciencedirect.com/science/article/pii/S0928098702000118
9. Vora N, Rana V. Preparation and optimization of mouth/orally dissolving tablets using a combination of glycine, carboxymethyl cellulose and sodium alginate: a comparison with superdisintegrants. Pharmaceutical development and technology. 2008 Jan 1;13(3):233-43. https://www.tandfonline.com/doi/abs/10.1080/10837450801949590
10. Hancock BC, Colvin JT, Mullarney MP, Zinchuk AV. The relative densities of pharmaceutical powders, blends, dry granulations, and immediate-release tablets. Pharmaceutical technology. 2003;27(4):64. https://elibrary.ru/item.asp?id=6291510
11. Jayakumar C, Morais A, Arunodhaya N, Gandhi N. Solubility enhancement of theophylline drug using different solubilization techniques. International Journal of Pharmaceutical and Clinical Science. 2012;2(1):7-10.