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ENHANCEMENT OF SOLUBILITY OF POORLY SOLUBLE DRUG BY USING SOLID DISPERSION TECHNIQUE

G. Srujana, M. Sai Pavan, P. Bhargav, S. Kanaka Durga, V. Lokesh Naidu, M. Sai Vishnu*, A. Lakshmana Rao
Department of Pharmaceutics
V. V. Institute of Pharmaceutical Sciences, Gudlavalleru, A.P.
E-mail: saivishnu13@gmail.com

ABSTRACT

The present work was aimed to Enhancement of solubility of Tinidazole by using solid dispersion technique by Solvent evaporation method. Tinidazole is a class II drug and it is poorly soluble in nature which is having long half life hence it is solubilized using solid dispersion technique to increase its solubility by using β-Cyclodextrin, Hydroxy propyl methyl cellulose, Polyethylene glycol 4000 and Polyethylene glycol 6000. Solid dispersions were prepared by mixing Tinidazole with β-Cyclodextrin, Hydroxy propyl methyl cellulose, Polyethylene glycol 4000 and Polyethylene glycol 6000 in different ratios. These dispersions were prepared by solvent evaporation technique according to composition given in Table 4. The ingredients like drug and carrier were accurately weighed (in different ratios 1:1, 1:2) and mixed in porcelain dish with a stirrer for 10minutes to get uniform mixture by employing ethanol as solvent. The residue was dried. This is sieved from sieve No 20 to obtain granules. The dispersion was then formulated as a capsule. The observed result reveals that carrier is having significant effect on drug release up to a larger extent.

Key words: Tinidazole, β-Cyclodextrin, Hydroxy propyl methyl cellulose, Polyethylene glycol 4000 and Polyethylene glycol 6000

INTRODUCTION

In pharmaceutical companies major work is going on in the field of drug discovery, in the anticipation of finding new therapeutic approaches and improving drugs for existing therapeutic areas. Among the five key physicochemical properties in the early compound screening including pka, solubility, permeability, stability and lipophilicity, poor solubility tops the list of undesirable compound properties.

Compounds with insufficient solubility carry a higher risk of failure during discovery and development since insufficient solubility may compromise other properties of compound and add undesirable properties[1] can influence both pharmacokinetic and pharmacodynamic properties of the compound and finally may affect the bioavailability of the compound. Therefore, there is need of a new approach for enhancing solubility of drug.

Solid dispersions[2]

The term solid dispersion refers to a group of solid products consisting of at least two different components, a hydrophilic matrix and a hydrophilic drug. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Pharmaceutical polymers are used to create this matrix and their selection is based on many factors, including physicochemical (e.g. rate of absorption) constraints. The solid dispersion components consist mainly of active pharmaceutical ingredients (API), the polymer, plasticizers, stabilizers, and other agents.

Advantages of solid dispersion[3]

The major advantages of solid dispersions is that it improves the dissolvability of a poorly water soluble drug in a pharmaceutical composition and results in rapid dissolution rates thereby improving the bioavailability of drug.

Rapid disintegration of oral tablets

Drug is formulated with hydrophilic carrier (eg PEG) as a solid dispersion to increase its aqueous solubility and dissolution .Then super disintegrant (eg croscarmellose sodium) is used in tablet formulation to achieve rapid disintegration of tablets prepared by wet granulation method. These rapidly disintegrating tablets can be used as an alternative to parenteral therapy enabling patient for self -medication even without the aid of water.

As a formulation vehicle

Solid dispersions can be used as formulation vehicle to facilitate the preclinical safety and early clinical studies on new chemical entities with very low aqueous solubility. It provides a means to rapidly assess the safety and efficacy profile of the drug substance that may be otherwise difficult to obtain.

Particles with reduced particle size

Solid dispersions represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers, thus a high surface area is formed, resulting in an increased dissolution rate and consequently improved bio availability.

Particles with improved wettability

Enhancement of drug solubility is released to the drug wettability. It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts when used, significantly increase the wettability of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.

Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity. Solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and therefore results in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release rate.

Drugs in amorphous state

The enhancement of drug release can usually be achieved if the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that if drugs precipitate it is as a met stable polymorphic form with higher solubility than the most stable crystal form.

Disadvantages of solid dispersion[4]

Disadvantages of solid dispersions are mainly related to their instability. Basically changes occur in several systems in crystallinity and a decrease in dissolution rate with ageing and system may be destabilized through physical treatment such as pulverization and ageing. There is more deteriorating effect f moisture and temperatures on solid dispersions that on physical mixture.

Usually solid dispersions are prepared with water soluble low melting point synthetic polymers such as polyvinyl pyrrolidone, mannitol or polyethylene glycol. These polymers show superior results in drug dissolution enhancement, but the amount of these polymers required is relatively large, around 1:2 to 1:8 (drug/polymer) ratio.

An obstacle of solid dispersion technology in pharmaceutical product development is that a large amount of carrier, i.e.; more than 50% to 80% w/w, is required to achieve the desired dissolution.

Solid dispersion is a high energy metastable form. Phase separation, crystal growth or conversion from the amorphous to the crystalline form during storage decrease solubility and dissolution rate and results in variable oral bioavailability.

Methods of preparation of solid dispersions

Various methods have been developed for preparation of solid dispersions, these methods deal with the challenge of mixing a matrix and a drug, preferably on a molecular level, while matrix and drug are generally poorly miscible. During many of the preparation techniques, demixing (partially or complete), and formation of different phases is observed. Phase separation like crystallization or formation of amorphous drug clusters are difficult to control and therefore unwanted.

1. Solvent evaporation method
2. Modified solvent evaporation method
3. Melting /fusion method
4. Solvent- melting method
5. Kneading method
6. Co-grinding method
7. Co-precipitation method
8. Spray drying method

9. Gel entrapment technique
10. Direct capsule filling
11. Lyophilization technique

The brief description of the methods is as follows:

1. Solvent evaporation method: After complete dissolution of drug and carrier in organic solvent, the solvent is evaporated. The solid mass is ground, sieved and dried. Prepared solid dispersions of ofloxacin with polyethylene glycol by solvent evaporation method[5].

MATERIALS AND METHODS

Tinidazole is an anti-parasitic drug used against protozoan infections. It is widely known throughout Europe and the developing world as a treatment for a variety of amoebic and parasitic infections. It was developed in 1972. A derivative of 2-methylimidazole, it is a prominent member of the nitroimidazole antibiotics.

A nitroimidazole antitrichomonal agent effective against Trichomonas vaginalis, Entamoeba histolytica, and Giardia lamblia infections.

Synonyms: Timidazole

Chemical Formula: $C_8H_{13}N_3O_4S$

Molecular weight: 247.273

Structure: Structure of Tinidazole is as shown in the Figure 1

Tinidazole is a classII drug and hence it is poorly soluble drug and which has longer half life hence it is formulated by using solid dispesion technique to increase solubility of the drug by using β-Cyclodextrin, HPMC, PEG 4000, PEG 6000. List of chemicals used in study and their manufacturers is shown in Table 1 and List of equipments used in study and their manufacturers is shown in Table 2.

Preformulation studies[6, 7]

Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable, efficacious and safe dosage form. Hence Preformulation studies were carried out on the obtained samples of drug for identification and compatibility studies.

Identification Test

The obtained sample was examined by infrared absorption spectral analysis and was compared with the reference standard IR spectrum of Tinidazole.

Determination of Melting Point

Melting point of Tinidazole was determined by open capillary method.

Solubility

Solubility is determined by taking small amount of sample in a test tube and solvent is added based upon dispersion of solid weather it is Freely Soluble, sparingly soluble, very slightly soluble.

Compatibility Studies

The compatibility of drug and carrier under experimental condition is important prerequisite before formulation. Incompatibility between drug and excipients can alter stability and bioavailability of drug, thereby, affecting its safety and efficacy. Study of drug–excipients compatibility is an important process in the development of a stable solid dosage form. Drug–excipients compatibility testing at an early stage Tinidazole in the selection of excipients that increases the probability of developing a stable dosage form.

Fourier Transform Infrared Spectroscopy (FTIR) studies

The drug- polymer and polymer-polymer interaction was studied by FTIR. Two percent (w/w) of the sample with respect to a potassium bromide disc was mixed with dry KBr. The mixture was ground into a fine powder using an agate mortar and then compressed into a KBr discs in a hydraulic press at a pressure of 10000 psi. Each KBr disc was scanned 16 times at 2 mm/sec at a resolution of 4 cm–1 using cosine apodization. The characteristic peaks were recorded. Ratio of Drug and Excipients taken for compatibility studies is shown in Table 3.

Estimation of Tinidazole

Determination of λmax of Tinidazole in 7.4 P^H Phosphate buffer

Stock solution: Standard stock solution was prepared by dissolving 100 mg drug in few drops of ethanol to it add 100ml of 7.4 P^H Phosphate buffer to get concentration of 1000 µg/ml. From this 1ml is taken in 10ml standard flask make up volume with 7.4 P^H Phosphate buffer to get concentration of 100 µg/ml.

Method development: Aliquots of stock solution was further diluted with 7.4 P^H Phosphate buffer to get working solution of 5, 10, 15, 20, 25µg/ml and the working standards were scanned between 200 - 400 nm which shows maximum absorbance at 317 nm. The same absorbance was used for the development of calibration curve.

Preparation of drug and carrier complex by using solvent evaporation method[6, 7]

Formulation 1

In china dish accurate weight of Tinidazole was taken to this add few ml alcohol. From this Specified amount of Tinidazole is taken for dissolution study.

Formulation 2

In china dish the drug Tinidazole and complexing agent β-cyclodextrin are taken in the proportion of 1:1.To this few ml of alcohol is added then drug is dispersed in solvent. Due to open evaporation a fine solid complex is formed.

Formulation 3

In china dish the drug Tinidazole and complexing agent β-cyclodextrin are taken in the proportion of 1:2.To this few ml of alcohol is added then drug is dispersed in solvent. Due to open evaporation a fine solid complex is formed.

Formulation 4

In china dish the drug Tinidazole and complexing agent HPMC are taken in the proportion of 1:1.To this few ml of alcohol is added then drug is dispersed in solvent. Due to open evaporation a fine solid complex is formed.

Formulation 5

In china dish the drug Tinidazole and complexing agent HPMC are taken in the proportion of 1:2.To this few ml of alcohol is added then drug is dispersed in solvent.

Due to open evaporation a fine solid complex is formed.

Formulation 6

In china dish the drug Tinidazole and complexing agent PEG 4000 are taken in the proportion of 1:1.To this few ml of alcohol is added then drug is dispersed in solvent. Due to open evaporation a fine solid complex is formed.

Formulation 7

In china dish the drug Tinidazole and complexing agent PEG 4000 are taken in the proportion of 1:2.To this few ml of alcohol is added then drug is dispersed in solvent. Due to open evaporation a fine solid complex is formed.

Formulation 8

In china dish the drug Tinidazole and complexing agent PEG 6000 are taken in the proportion of 1:1.To this few ml of alcohol is added then drug is dispersed in solvent. Due to open evaporation a fine solid complex is formed.

Formulation 9

In china dish the drug Tinidazole and complexing agent PEG 6000 are taken in the proportion of 1:2.To this few ml of alcohol is added then drug is dispersed in solvent. Due to open evaporation a fine solid complex is formed.

Design

F1, F2, F3, F4, F5, F6, F7, F8 and F9 were designed to optimize the concentrations of β- cyclodextrin, HPMC, PEG 4000, PEG 6000 and to study the effect of beta cyclodextrin, HPMC, PEG 4000 and PEG 6000.

The prepared dispersions are taken from each formulation. These formulations are passed through sieve no: 20 to obtain granules. From these formulation drugs quantity equal to 100mg is weighed. These are filled into the capsules and those solid dispersions are evaluated. Optimization of formulation ingredients in preparation is shown in Table 4.

Evaluation parameters [8, 9]

***In-vitro* Dissolution studies of solid dispersions:** Dissolution studies were carried out for all the formulations combinations in triplicate, employing USP II paddle method and 900ml of distilled water as the dissolution medium. The medium was allowed to equilibrate to temp of 37°c + 0.5°c. Solid dispersion was placed in the vessel and the vessel was covered the apparatus was operated for 1 hrs in distilled water at 50 rpm. At definite time intervals of 5 ml of the aliquot of sample was withdrawn periodically and the volume replaced with equivalent amount of the fresh dissolution medium. The samples were analyzed spectrophotometrically at 317nm using uv-spectrophotometer.

Release Kinetics: The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of dispersion systems. As a model-dependent approach, the dissolution data was fitted to popular release models such as zero-order, first-order equations, which have been described in the literature. The order of drug release from dispersions was described by using zero order kinetics (or) first orders kinetics.

RESULTS AND DISCUSSION

Solubility

Solubility of Tinidazole is very slightly soluble in water, sparingly soluble in methanol and ethanol, freely soluble in acetone and acetic anhydride.

Drug excipient compatibility studies

FTIR spectra of pure drug

FTIR spectra of pure drug are shown in Figure 2 and Interpretation of pure drug functional groups and characteristic absorption is shown in Table 5.

FTIR spectra of Drug and β-Cycloderxtrin

FTIR spectra of Drug and β-Cycloderxtrin are shown in Figure 3.

Discussion

There is no change in the nature and position of the characteristic band for the drug and drug-polymer used in the formulation, it can be concluded that there is no chemical interaction between the drug and polymer.

FTIR spectra of Drug and PEG 6000(Optimized formulation)

FTIR spectra of Drug and PEG6000 (optimized formulation) are shown in Figure 4. **Discussion**

There is no change in the nature and position of the characteristic band for the drug and drug-polymer used in the formulation, it can be concluded that there is no chemical interaction between the drug and polymer.

Standard curve of Tinidazole

Series of concentrations and their absorbance are as shown in Table 6. Calibration curve of Tinidazole is as shown in Figure 5.

Discussion

Based on above results, it has been inferred that API shows linearity in concentration range of 5-25µg/ml. the regression coefficient of calibration curve was found to be 0.9997.

***In vitro* dissolution**

Dissolution data and comparative studies of all formulations are shown in Table 7. Comparitive profile of all formulas F1to F9 are shown in Figure 6.

Discussion

Increase in concentration of different polymers such as the β-Cyclodextrin, HPMC, PEG 4000, PEG 6000 increased in drug release. Higher the amount of polymer, greater is the driving force to release the drug. This is because increase in polymer concentration the resultant complex is more soluble thus release is increased. And from above results PEG 6000 used formulation release up to 98.95% in 1hr but others such as β-cyclodextrin used polymer release up to 33.83% at 1hr, HPMC used polymer release up to 59.42% at 1hr, PEG 4000 used polymer release up to 77.09% at 1hr and hence PEG 6000(1:2) used is considered as optimized formulation.

Dissolution – application of kinetics

Zero order plot for optimized formula is shown in Figure 7, First order plot for optimized formula is shown in Figure. No 8 and Kinetic data of optimized formula (F9) are shown in Table 8.

Discussion

From the regression valve closer to unity in case of first order (R^2=0.9881) the release is apparently first order. As clearly indicated the release of the drug followed first order release kinetics and regression valve indicates fair of linearity in the data. This shows that the release is dependent on the concentration of drug. When plotted according to the zero order equation, the data indicated poor linearity as represented by regression valvesR^2=0.914. Hence this optimized formulation is used for formulation of fast dissolving tablets.

CONCLUSION

We can conclude that this formulation development was designed to enhance the drug solubility in order to formulate fast dissolving that dispenses drug in fast release manner with in therapeutic concentrations.

The results generated in this study showed that the profile and kinetics of drug release were the functions of polymer type and polymer concentration.

β-Cyclodextrin > HPMC > PEG-4000> PEG-6000

Thus the PEG-6000 used solid dispersions attain the fast release dispersion than that of other polymers such as β-Cyclodextrin, HPMC and PEG-4000.

Hence β-Cyclodextrin, HPMC polymer dispersions are used for the formulation of controlled release dosage forms and PEG-4000, PEG-6000 polymer dispersions are used for the formulation of fast dissolving dosage forms

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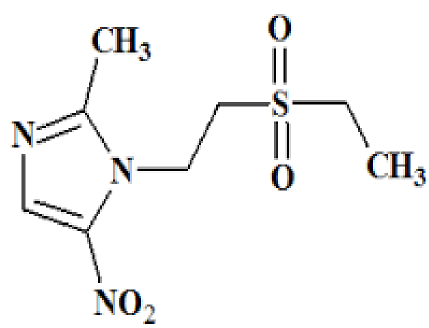

Figure 1: Structure of Tinidazole

Table 1: List of chemicals used in study and their manufacturers

S. No	CHEMICALS	MANUFACTURER	PURPOSE
1	Tinidazole	Yarrow chem products	API
2	β-Cyclodextrin	Yarrow chem products	Carrier
3	PEG 4000	Darvin	Carrier
4	PEG 6000	Darvin	Carrier
5	HPMC	Yarrow chem products	Carrier
6	Ethanol	Delta	Solvent
7	Distilled water	Institutional supply	Solvent

Table 2: List of equipments used in study and their manufacturers

S. No	EQUIPMENT	MANUFACTURER

1.	Electronic balance	Infra instrument pvt .Ltd-Chennai
2.	Dissolution apparatus USP2	Labindia
3.	Hot air oven	Darvin
4.	U.V spectrophotometer	Shimadzu UV-1800 Double beam spectrophotometer

Table 3: Ratio of Drug and Excipients taken for compatibility studies

Ingredients	Ratio of Drug and Excipients
Tinidazole	1:0
Tinidazole + β-Cyclodexrin	1:1
Tinidazole + PEG 6000	1:1

Table 4: Optimization of formulation ingredients in preparation

S. No	Formulation	Drug	Carrier	Composition	Solvent (ethanol)
1.	F1	100mg	-------	-------	-------
2.	F2	1000mg	β-cyclodextrin	1 : 1	5-10ml
3.	F3	1000mg	β-cyclodextrin	1 : 2	5-10ml
4.	F4	1000mg	HPMC	1 : 1	5-10ml
5.	F5	1000mg	HPMC	1 : 2	5-10ml
6.	F6	1000mg	PEG 4000	1 : 1	5-10ml
7.	F7	1000mg	PEG 4000	1 : 2	5-10ml
8.	F8	1000mg	PEG 6000	1 : 1	5-10ml
9.	F9	1000mg	PEG 6000	1 : 2	5-10ml

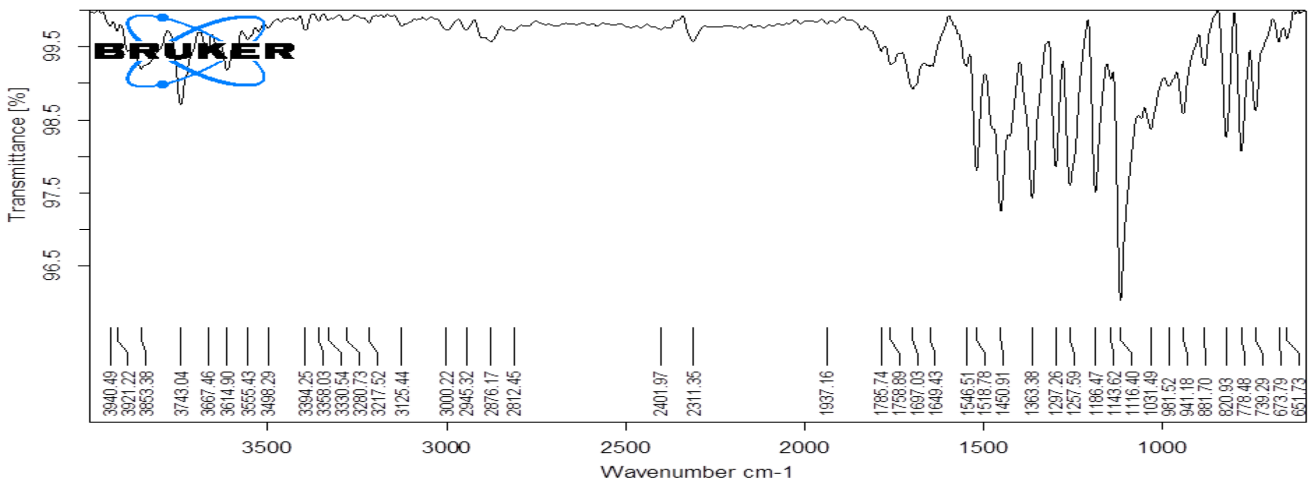

Figure 2: FTIR spectra of pure drug

Table 5: Interpretation of pure drug functional groups and characteristic absorption

S. No	Functional group	Characteristic absorption
1.	C=N	1518
2.	N=O	1546
3.	S=O	1143
4.	CH_3	1363
5.	C-N	1031
6.	C=C	1649

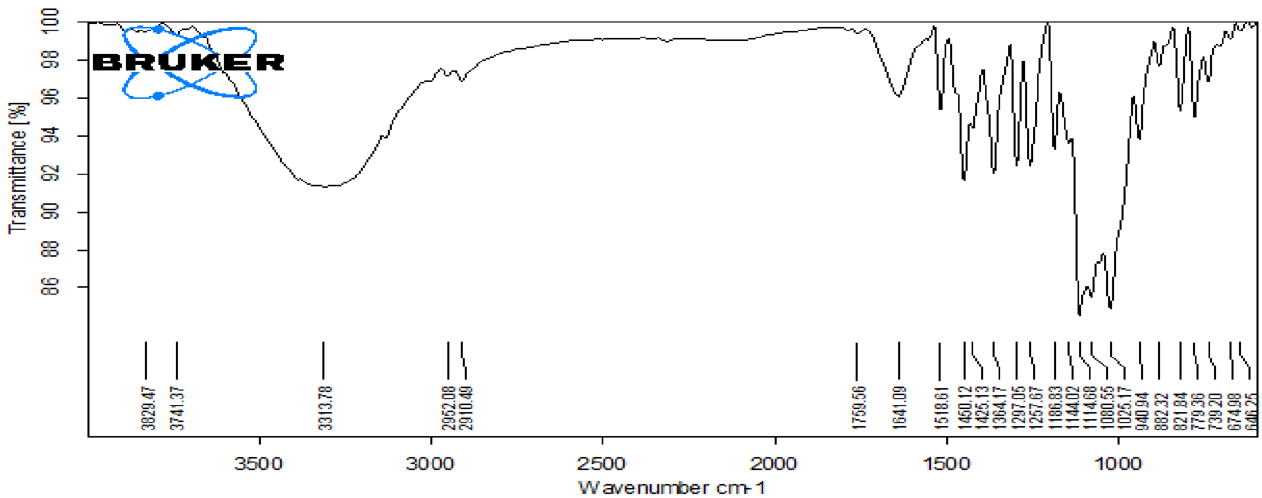

Figure 3: FTIR spectra of drug and β-Cyclodextrin

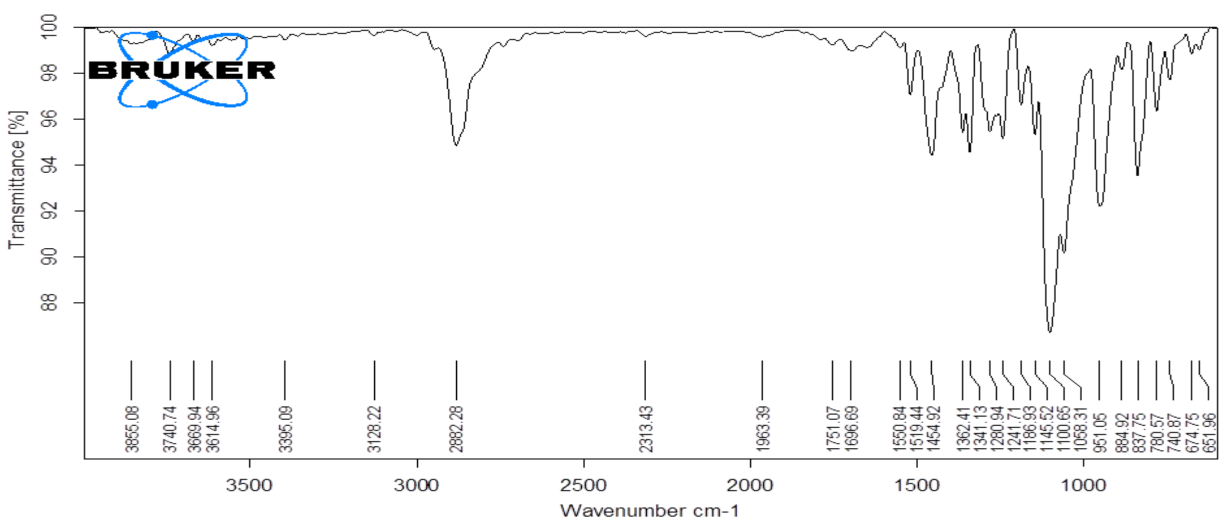

Figure 4: FTIR spectra of Drug and PEG6000 (optimized formulation)

Table 6: Series of concentrations and their absorbance

Concentration (µg/ml)	Absorbance
0	0
5	0.232
10	0.5
15	0.723
20	0.871
25	1.20

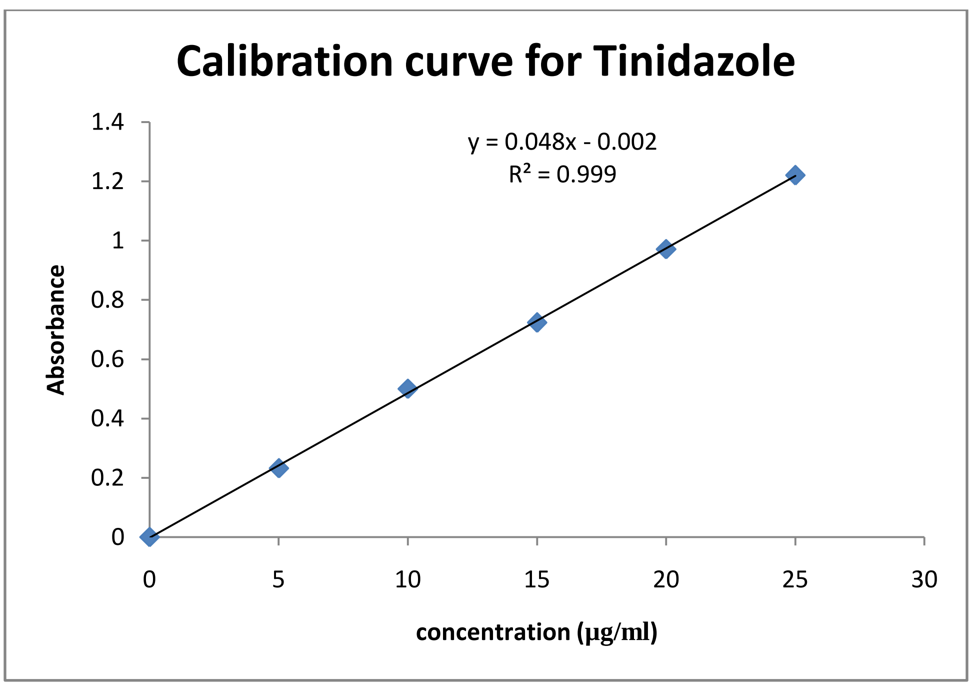

Figure 5: calibration curve of Tinidazole

Table 7: Dissolution data and comparative studies of all formulations

S. No	Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	0	0	0	0	0	0	0	0	0	0
2.	10	6.78	12.43	16.51	8.81	8.59	10.62	26.69	24.43	28.28
3.	20	12.4	14.31	23.84	12.93	17.01	38.06	47.2	38.59	55.81
4.	30	13.5	16.61	27.17	27.269	31.81	56.14	54.25	56.67	77.15
5.	40	14.68	20.14	29.1	35.56	41.94	64.37	73.77	64.22	88.21
6.	50	15.6	24.09	31.48	45.71	52.35	67.21	76.67	70.68	97.75
7.	60	15.4	26.94	33.83	55.014	59.42	69.84	77.09	72.64	98.95

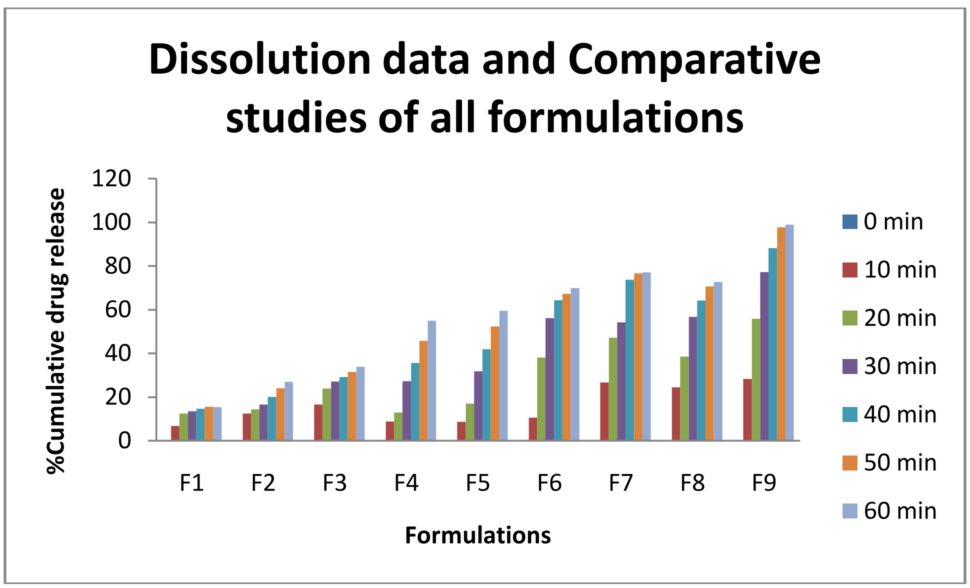

Figure 6: Comparitive profile of all formulas F1to F9

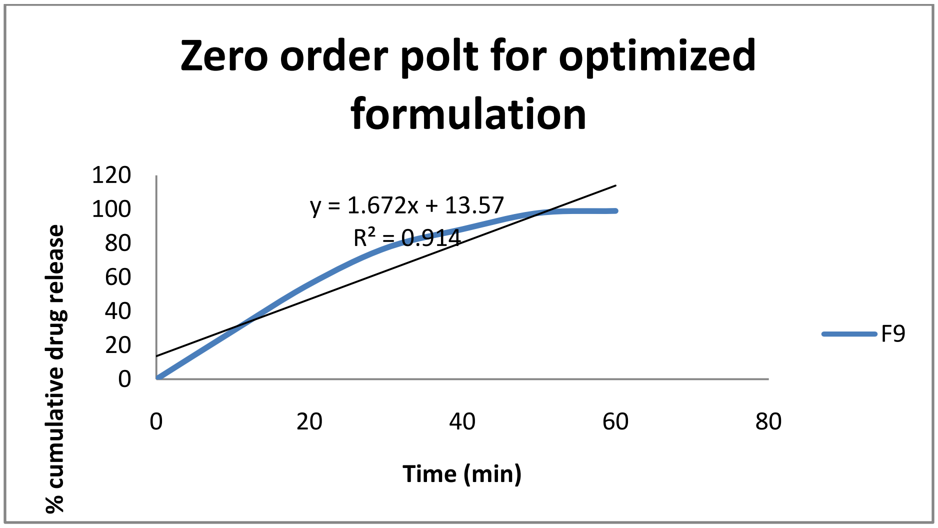

Figure 7: Zero order plot for optimized formula

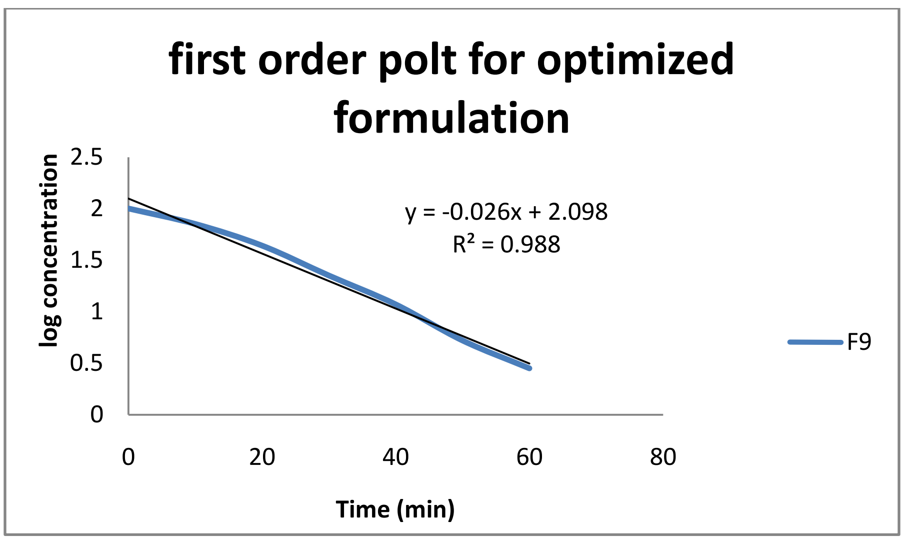

Figure 8: First order plot for optimized formula

Table 8: Kinetic data of optimized formula (F9)

PLOT	Regression R^2
Zero order plot	0.9148
First order plot	0.9881