FORMULATION AND EVALUATION OF ORODISPERSIBLE LIQUISOLID COMPACTS OF KETOCONAZOLE USING CO-PROCESSED SUPERDISINTEGRANTS

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ABSTRACT

Objective: Drug dissolution is a rate limiting step for the bioavailability of many BCS Class II drugs. The bioavailability of such drugs can be improved by the application of various solubility enhancement techniques. Liquisolid technique is a novel technique. It is used to improve the dissolution rate of the poorly water soluble drugs like Ketoconazole. The aim of the present study was to enhance the dissolution of a practically insoluble Ketoconazole by liquisolid compact technique and to enhance the onset of action by Orodispersible tablet technique.

Materials and methods: Orodispersible liquisolid compact of Ketoconazole were prepared by using PEG 400, Microcrystalline cellulose PH 102 and Aerosil 200 as non-volatile solvent, carrier, coating material respectively and co-processed superdisintegrants (Crosspovidone and croscarmellose sodium) in the ratio of 1:1, 1:2, 1:3.

Results: Orodispersible liquisolid compacts of Ketoconazole tablets (F6) containing co-processed superdisintegrants in the ratio of 1:3 exhibits quick disintegration time and maximum drug release

Conclusion: This research work may be useful to formulate Orodispersible tablets using Liquisolid technique which may give rapid onset of action by rapid absorption, maximize efficacy and hence increase patient compliance.

Keywords: Orodispersible Liquisolid compacts, poorly soluble drugs, co-processed super-disintegrants, dissolution rate, bioavailability

INTRODUCTION

Therapeutic efficiency of a drug is dependent on the bioavailability and eventually upon the solubility and absorption of drug molecules [1,2]. The solubility is an important parameter to achieve the required concentration of drug in the systemic circulation and hence to attain the biological activity of the drug in the body. As a matter of fact, more than one-third of the drugs listed in the U.S. Pharmacopoeia fall into the poorly water-soluble or water-insoluble categories.[3] The solubility issues can affect the oral delivery of the new drugs and also the delivery of many existing drugs.

The drugs with poor solubility exhibit many in vitro formulation related difficulties, such as restricted choices of delivery of drug and highly complex dissolution testing with inadequate correlation to the in vivo absorption[4].These types of issues with in vivo and in vitro characteristics and the problems in attaining expected and reproducible in vivo/in vitro correlations (IVIVC) are often due to solubility issues with many newly synthesized compounds Hence, it is essential to improve the solubility of such drugs by applying different solubility enhancement techniques[5].These active pharmaceutical ingredients (APIs) often suffer from formulation challenges because of limited dissolution and low permeability. Accordingly; applicable formulation techniques are highly aspired to improve the apparent solubility or dissolution of poorly soluble drugs and thus enable them become bioavailable.[6]

LIQUISOLID SYSTEM

The liquisolid technology is described by Spireas as liquid may be transformed into a free-flowing, readily compressible, and apparently dry powder by simple physical blending with selected excipients named the carrier and coating material. The liquisolid technique is a novel approach for delivery of drugs through the oral route. This technique is suitable for poorly soluble or water insoluble drugs, highly permeable drugs (BCS Class II drugs) and also for immediate or sustained release formulations. A liquid lipophilic drug can be converted into liquisolid system without being further modified. On the other hand, if a solid water-insoluble drug is formulated, it should be initially dissolved or suspended in suitable nonvolatile solvent system to produce drug solution or drug suspension of desired concentration. Inert, preferably water-miscible organic solvent systems with high boiling point and a not highly viscous organic solvent system such as propylene glycol, liquid polyethylene glycols, polysorbates, fixed oils, or glycerin are best suitable as liquid vehicles[7].

It is a novel "Powder Solution Technology" that involves absorption and adsorption efficiencies, making use of liquid medications, drug suspensions admixed with suitable carriers, coating materials and formulated into free flowing, dry looking, and non-adherent and compressible powder forms. Improvement in bioavailability may be due to increased surface area, increased aqueous solubility and increased the wettability of the drug. Liquisolid technique also has the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems.

Overall, liquisolid technique is a most promising and novel technique for enhancing the dissolution and bioavailability of poorly water soluble drugs and sustaining drug release from tablet matrix. The liquisolid compacts are regarded as acceptably flowing and compressible powdered forms of a liquid medication. The latter include liquid lipophilic drugs or solid water-insoluble drugs dissolved in suitable water miscible non-volatile solvents [8].

ORODISPERSIBLE TABLETS

For the past one decade, there has been an enhanced demand for more patient-friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing annually. Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency and the production of more cost-effective dosage forms.[9]

Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available. However, many patient groups such as the elderly, children and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid-intake/diets have difficulties swallowing these dosage forms. Those who are traveling or have little access to water are similarly affected [20] . To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as "Orally Disintegrating Tablets (ODT)" which disintegrate rapidly in saliva, usually in a matter of seconds, without the need of water. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms [10].

ODTs can be used easily in children who have lost their primary teeth but do not have full use of their permanent teeth [22].Description of orally disintegrating (OD) dosage forms All fast disintegrating tablets approved by United States Food and Drug Administration (US FDA) are classified as "ODTs". European Pharmacopoeia adopted the term "orodispersible tablets" for tablets that dispersed or disintegrate in less than 3 min in the mouth before swallowing. Such a tablet disintegrates into smaller granules or gel like structure, allowing easily swallowing by patients. As per recent US FDA guideline on ODT, disintegration time of ODT should have an in vitro disintegration time of approximate 30 s or less, when based on United States Pharmacopoeia (USP) disintegration test method or alternative[11].ODTs are different from conventional sublingual tablets, buccal tablets and lozenges, which require more than a minute to dissolve in oral cavity.

KETOCONAZOLE [12]

Ketoconazole is an imidazole synthetic derivative of phenylpiperazine with broad antifungal properties and potential antineoplastic activity. Ketoconazole inhibits sterol 14-a-dimethylase, a microsomal cytochrome P450-dependent enzyme, thereby disrupting synthesis of ergosterol, an important component of the fungal cell wall. It is the first orally effective broad-spectrum antifungal drug, useful in both dermatophytosis and deep mycosis.

MATERIALS AND METHODS

MATERIALS

Ketoconazole was kindly gifted by UNIX BIOTECH Himachal Pradesh (India), Polyethyleneglycol-400, Microcrystalline cellulose PH102, Aerosil 200, Mannitol, Crosspovidone, Croscarmellose sodium, Magnesium stearate, Talc was purchased from Central Drug House, New Delhi (India). All reagents and chemicals were of analytical grade.

METHOD

Determination of absorbance maxima (λmax) by UV

To determine absorbance maxima of drug, stock solution was prepared by dissolving 25 mg of drug in 25ml of to get concentration of 1mg/ml (1000 µg/ml) solutions.

From the stock solution, dilution of 10µg/ml was prepared and analyzed by UV between 200-400nm to obtain maximum wavelength of drug[13].

Standard curve of ketoconazole in different solvents

100 mg of drug was accurately weighed and dissolved in 100 ml 0.1N HCL, phosphate buffer pH 6.8**,** Methanol separately to get a concentration of 1mg/ml.This solution was marked as the stock solution. From stock solution dilutions having concentration 0.5µg/ml, 1.0 µg/ml, 1.5µg/ml, 2 µg/ml, 2.5 µg/ml, 3 µg/ml,3.5 µg/ml,Beer's range 5-35 µg/ml) was prepared. These dilutions were observed in UV Spectrophotometer and absorbance was measured[14].

Identification of Drugs

The identification of the drug was done by (FT-IR) spectroscopic method using Alpha Bruker FTIR spectrophotometer. The drug was mixed with suitable amount of KBr and converted into pellets using KBr press at 20 psi for 10 min. The disc thus prepared was placed in a sample compartment and scanned at transmission mode in the region of 4000 to 400 cm-1 . the wave numbers of peaks in IR spectrum of the drug thus obtained was compared with the theoretical values of the wavenumber corresponding to the structure of drugs[15].

Drug Excipients Compatibility Study

Before formulating a dosage form it is very necessary to confirm that drug is not interacting with the polymer under certain experimental conditions. Interaction among drug and polymer may affect the efficacy of final dosage form. Drug and excipients were accurately weighed and mixed and the resulting mixtures were scaled in screw glass vials and kept at a 50°C for 15 days. [16]

Solubility studies for the selection of non-volatile solvents

Solubility studies are carried out by preparing saturated solutions of drug in non-volatile solvent (propylene glycol, Tween 80 and polyethylene glycol 400, Polysorbate 80) and analyzing them spectrophotometrically .Saturated solutions are prepared by adding excess of drug to non volatile solvent and shaking them for 24 hrs at 25 ˚C. After 24 hrs, the saturated solutions were filtered and analyzed by UV spectrophotometer at 270 nm[17].

Calculation of loading factor

Loading factors were calculated for carriers, for the non-volatile solvents PEG 400.

By using Lf = W/Q formula (W: Amount of liquid medication and Q: Amount of carrier material), the drug loading factors were obtained and used for calculating the amount of carrier and coating materials in each formulation[18].

Preparation of Co-Processed Superdisintegrants

The co-processed Superdisintegrants were prepared by solvent evaporation method. A blend of crospovidone and croscarmellose sodium (in the ratio of 1:1, 1:2 & 1:3) was added to 10 ml of ethanol. The contents of the beaker (250 ml capacity) were mixed thoroughly and stirring was continued till most of ethanol gets evaporated. The wet coherent mass was granulated through # 44-mesh sieve. The wet granules were dried in a hot air oven at 60º C for 20 minutes. The dried granules were sifted through #44- mesh sieve and stored in airtight container till further use.

FORMULATION OF ORODISPERSIBLE LIQUISOLID COMPACTS

Various liquisolid ODTs formulas containing 100 mg of Ketoconazole were prepared by dispersing the drug in the non-volatile vehicle (PEG-400). Then a binary mixture of carrier (Avicel PH 102) and coating material (Aerosil 200) was prepared at a ratio of 5:1(R=5) for F-I to F-III and 10:1(R=10) for F IV to F-VI and 15:1(R=15) for F-VII to F-IX. The carrier material was added to the admixture of drug and vehicle and triturated well and waited for 10 minutes in order to complete absorption of liquefied drug in the porous carrier material .Then, weighed amount of coating material was added and triturated slowly for 15 minutes for the complete adsorption of coating material over the porous carrier material. Finally, co-processed superdisintegrant and other excipients were added to the above powder blend and mixed thoroughly. The final powder blend was subjected to direct compression by using 8mm flat upper-scoring punch on fluid pack- 12 station punching machine. The formulas F-I to F-III were prepared by using the excipients ratio R=5 and 1:1, 1:2, 1:3 ratio of co-processed Superdisintegrants. The loading factor was kept constant in the above formulas which is equal to 0.804; the formulas F-IV to F-VI were prepared using the excipients ratio R=10 and 1:1, 1:2, 1:3 ratio of co-processed Superdisintegrants. The loading factor was kept constant in the above formula which is equal to 0.67. the formulas F-VII to F-IX were prepared using the excipients ratio R=15 and 1:1, 1:2, 1:3 ratio of co-processed Superdisintegrants. The loading factor was kept constant in the above formula which is equal to 0.5742.

EVALUATION OF POWDER BLEND

The prepared powder blend were subjected to evaluation as per the methods suggested in the Indian Pharmacopoeia like Bulk density, Tapped density, Hausner's ratio, Angle of repose and car's index.

Angle of repose

The angle of repose of the powder blend was determined by using funnel method. The accurately weighed powder was taken in a funnel. The height of funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The diameter of the powder cone was measured and angle of repose was calculated by using the equation [19].

$$\mathbf{Tan\ \theta = h/r}$$

Where, h and r are the height of pile and radius of the pile.

Bulk density [20]

Bulk density Ketoconazole of was determined by pouring gently 5.00gm through a glass funnel into 20 ml graduated cylinder. The volumes occupied by the samples were recorded. Bulk density was calculated as:

Bulk density = weight of sample in gram /volume occupied by the sample

Tapped density[21]

Tapped density was determined by using LABINDIA density tester, which consists of a graduated cylinder mounted on a mechanical tapping device. An accurately weighed sample of powder was carefully added to the cylinder with the aid of a funnel. Typically, the initial volume was noted, and the sample is then tapped (50, 100,150 or 250 tapping) until no further reduction in volume is noted or the percentage of difference is not more than 2%.

A sufficient number of taps should be employed to assure reproducibility for the material in question. Volume was noted and tapped density is calculated using following formula.

Tapped density = Wt. of sample in gm / Tapped volume

Compressibility Index and Hausner's ratio[22]

In recent years the compressibility index and the closely related Hausner's ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. Both the compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of a powder.

Carr' s index =Tapped density-Bulk density/ Tapped density ×100

Hausenr's Ratio = Tapped Density / Bulk Density

EVALUATION OF TABLETS: (POST COMPRESSION PARAMETER)

Weight Variation

20 intact tablets were selected randomly and weighed ,the average weight was calculated. Individual weight of each tablet was determined. According to USP, none of the individual tablet weight should be less than 90% and more than 110% of the average weight[23].

Hardness

Take 10 tablets from the sample given for analysis, test the Hardness in Kg/Cm2 for each tablet and note down the results. Calculate the average of the 10 readings and report the average result.
Acceptance criteria: Not less than 4.0 Kg/cm2.

Thickness

The thickness of the tablets was determined using digital caliper; reading shown was noted. The hardness was tested by using Monsanto tester[24].

Friability (core tablets)

Take 13 tablets from the sample given for analysis and de-dust. Weigh the tablets and note down the weight. Place the tablets in the drum of the friability apparatus and set the apparatus rotation time for 4 minutes (100 revolutions). Operate the instrument for the specified time or for the rpm. Take out the tablets and de-dust.
Weigh the tablets and calculate the friability by the following formulae[25].

$$\text{Friability (\%)} = \frac{\text{(Initial weight of the tablets – Final weight of the tablets) x 100}}{\text{Initial weight of the tablets}}$$

Acceptance criteria: Friability is not more than 1.0 %

Compatibility studies

Compatibility studies were carried out using Fourier Transform Infra red spectroscopy to detect any possible interaction of ketoconazole with the excipient used in the formulation.
The FTIR spectra of the formulations were compared with the FTIR spectra of the pure drug.(400 cm-1 - 4000cm-1). The results indicated that the characteristic absorption peaks due to pure ketoconazole have appeared in the formulated liquisolid compact, without any significant change in their position after successful encapsulation [26].

In-vitro dispersion time

In-vitro dispersion time was measured by following procedure. The tablet was carefully positioned in the center of the petridish containing 6 ml of water and the time required for the tablet to completely disintegrate into fine particles was noted. Three tablets from each formulation were randomly selected and Invitro dispersion time was measured[27].

In-vitro Disintegration Time

Fill the beakers with water and switch on the Apparatus and wait for some time to reach the desired temperature (37 0 C).When the apparatus reaches to the desire temperature, the siren is coming from the apparatus. Place the 6 tablets in each case of the basket. Water at 37 ± 2˚C was used as a disintegration media Press start for disintegration and the time taken for complete disintegration of the tablet was noted with no passable mass remaining in the apparatus was measured[28].

Wetting time

A piece of tissue paper was folded twice and placed in small petri dish containing sufficient water. A tablet was kept on the paper and the time for complete wetting of tablet was measured[29].

Water absorption ratio

The weight of the tablet prior to placement in the petri dish was noted (Wb). The wetted tablet was removed and reweighed (Wa). Water absorption ratio R, was then determined according to the following equation.

$$R = 100 \times (Wa - Wb)/Wb$$

Where Wb and Wa are tablet weights before and after water absorption, respectively[30].

Uniformity of dispersion

Two tablets were kept in 100ml water and stirred gently for 2 minutes. The dispersion was passed through 22 meshes. The tablets were considered passing the test if no residue remained on the screen [31].

Drug content determination

Three tablets were selected randomly and average weight was calculated. Tablets were crushed in a mortar and accurately weighed amount of tablet powder was taken from the crushed blend and transferred it in to a 100 ml volumetric flask.10 ml of methanol was added and sonicated for 10 minutes. Then volume was made up to 100 ml with pH 7.4 buffer. The 1mL of resultant solution was diluted to 100mL with buffer (pH 7.4). The absorbance of above solution was measured in UV spectrophotometer at 237nm[32].

Dissolution Studies (In Vitro Drug Release Studies)

The Model drug release from different formulations was determined using aUSP-type2 (paddle type) apparatus under sink condition. The dissolution medium was 900ml Phosphate buffer pH 7.4 at 37 ± 0.5°C; and 50rpm, to simulate in vivo conditions. The formulation prepared was subjected to dissolution tests for 1hrs. Sample (5ml) was withdrawn at predetermined time intervals (5, 10,15,20,25, 30,35,40 45, 55,60,), filtered through Whatmann filter paper and replaced by an equal volume of dissolution medium. Drug content in the dissolution sample was determined by UV spectrophotometer at 270 nm[33]

Apparatus : USP-2, paddle method
Dissolution Medium : 0.01 N HCl
rpm : 50
Time intervals : 5, 10, 15, 20,25,30,35,40, 45, 50,55,60,
Temperature : 37 ± 0.50 C

Drug release kinetic study

The drug release kinetic specifies the release mechanism of drug from liquisolid compact.
The obtained release data was treated using following equation
Zero order equation- the graph plotted between amounts of drug release versus time.
First order equation- graph between log cumulative percent of drug remaining versus time. Higuchi equation- graph between cumulative percent of drug release versus square root of time. Korsmeyer-Peppas equation- graph between log cumulative percent of drug release versus log time[34].

RESULTS AND DISCUSSIONS

Liquid load factor

Loading factors were calculated for different ratio of carriers and coating using PEG 400 as vehicle. The loading factor for the R value 10 and 15 was found to be 0.205 and 0.138 respectively.

Table No.1. liquid load factor

S. N o	Liquid vehicles	Carrier and coating Material ratio	Liquid load factor
1.	P e g 4 0 0	1 :5	0.804
2.	P e g 4 0 0	1 :1 0	0.67
3.	P e g 4 0 0	1 :15	0.574

UV spectroscopy determination of absorbance maxima

As per the observed data the absorption maxima of ketoconazole was found to be 270 nm which comply with standard value.

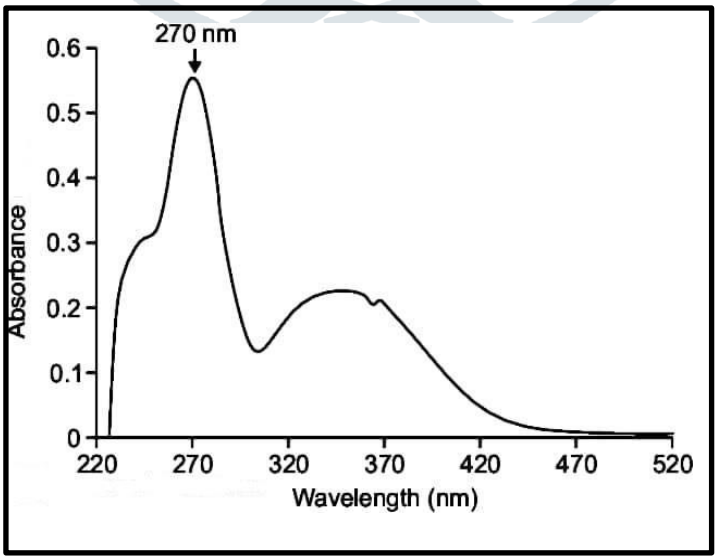

Fig 1. Absorption maxima of ketoconazole

Standard curve of ketoconazole in different solvents

Standard curve of ketoconazole in 0.1N HCL

Table No.2. Standard curve data of ketoconazole in different solvents

Sr. No.	Concentration (µg/ml)	Absorbance(nm)		
		Phosphate buffer pH. 6.8	0.1 n HCl	Methanol
1	**0**	**0**	**0**	**0**
2	0.5	0.1235	0.1621	0.132
3	1	0.2781	0.2931	0.3018
4	1.5	0.3941	0.4129	0.4334
5	2	0.5191	0.5731	0.5501
6	2.5	0.6732	0.7268	0.7156
7.	3	0.8358	0.8319	0.8432
8.	3.5	0.9961	0.9935	0.9961

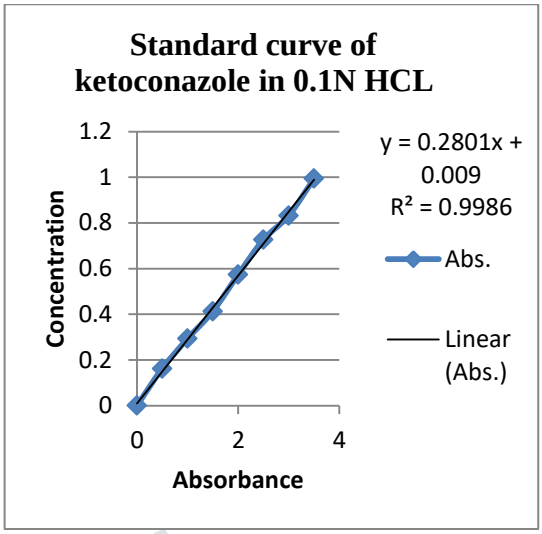

Fig 1. Standard curve of ketoconazole in 0.1N HCL

Standard curve of ketoconazole in Methanol

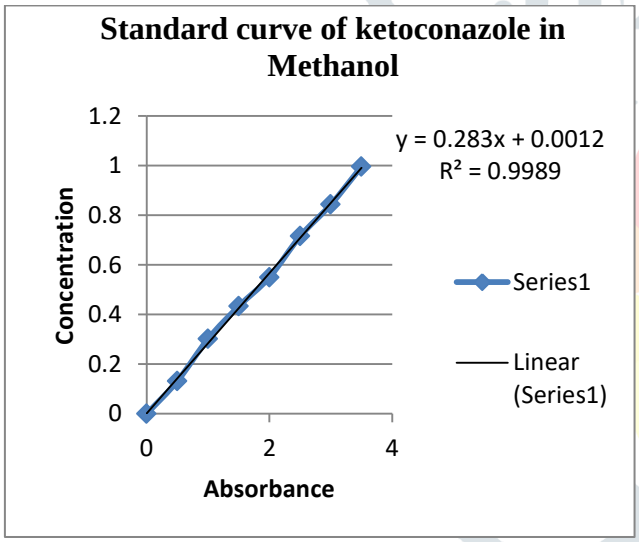

Fig 2. Standard curve of ketoconazole in Methanol

Standard curve of ketoconazole in phosphate buffer pH 6.8

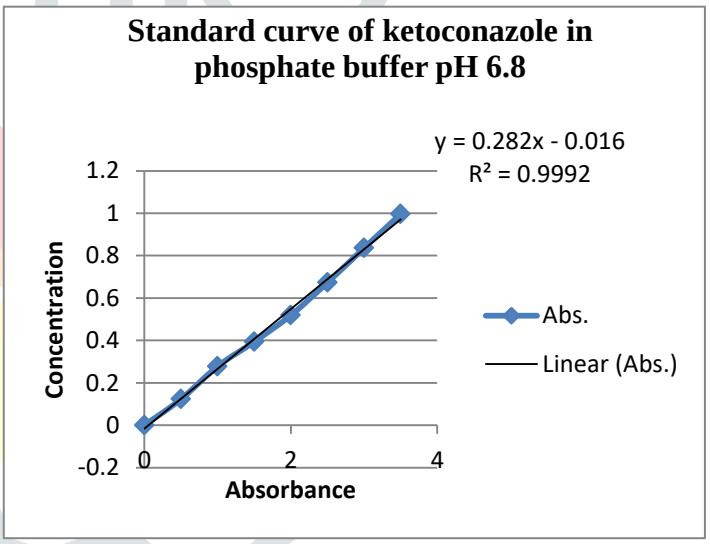

Fig 3.Standard curve of ketoconazole in phosphate buffer pH6.8

Drug Identification

By infra-red spectrum method: Drug and polymers identified by infra-red spectrum which are compared with its standard IR. The IR spectrum given below shown that the peaks obtained in the test spectrum is similar to that given in standard.

The IR spectrum of ketoconazole revealed the presence of peak at 3085.89 cm–1 due to N-H stretching while peaks at 2927.74 and 2740.66 cm–1 is due to aliphatic C-H stretching. Strong absorption peaks observed at 1743.53 and 1689.53 cm–1 were assigned to drug carbonyl stretching vibration (C=O). A peak at 1612 cm–1 indicates the aromatic ring and a peak at 1238 cm–1 is due to C-O Ar group. Peaks obtained in spectrum of pure drug were similar to that given in standard.

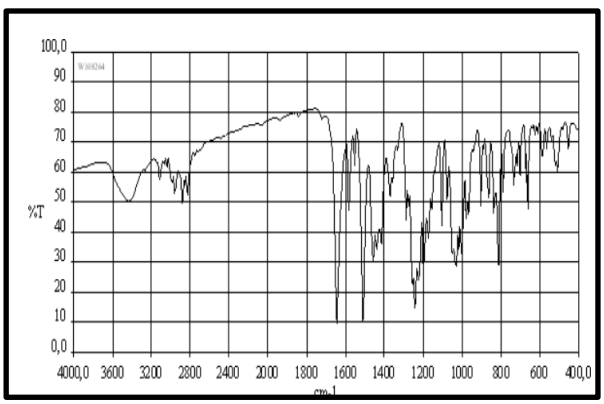

Fig 4. Reference FTIR spectrum of ketoconazole

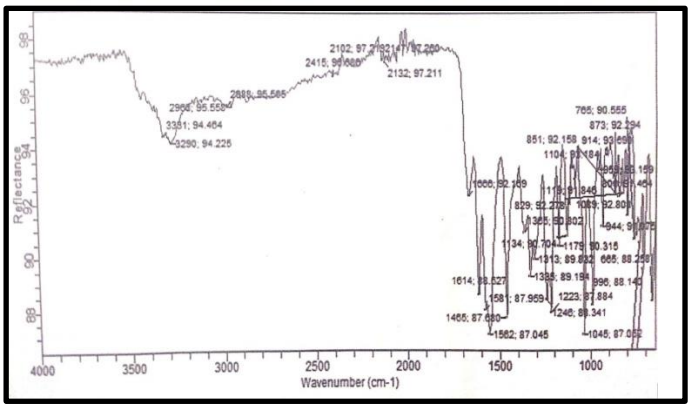

Fig 5. FTIR spectrum of ketoconazole

Drug excipients compatibility study by FTIR

The drug-polymer interactions shows that there was no major shifts in the absorption band(peaks) of in presence of polymer and it was observed that all the characteristics peaks of drug in present in the combination of drug and polymer spectra indicating the compatibility of drug with the polymer used.

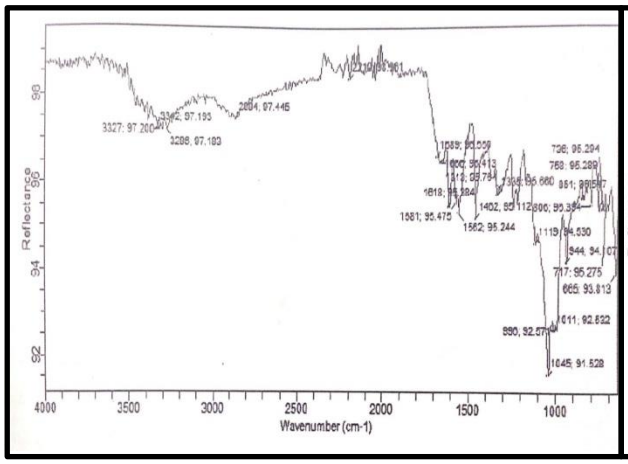

Fig 6. FTIR spectrum of Ketoconazole + Crospovidone

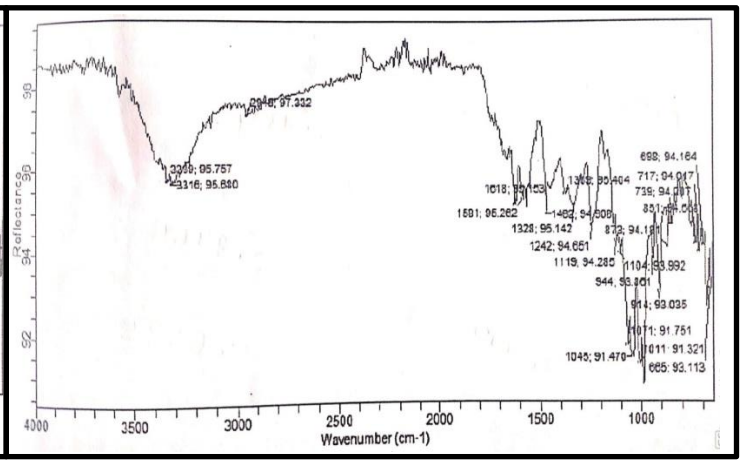

Fig 7. FTIR spectrum of Ketoconazole+ + Crosscarmellose sodium

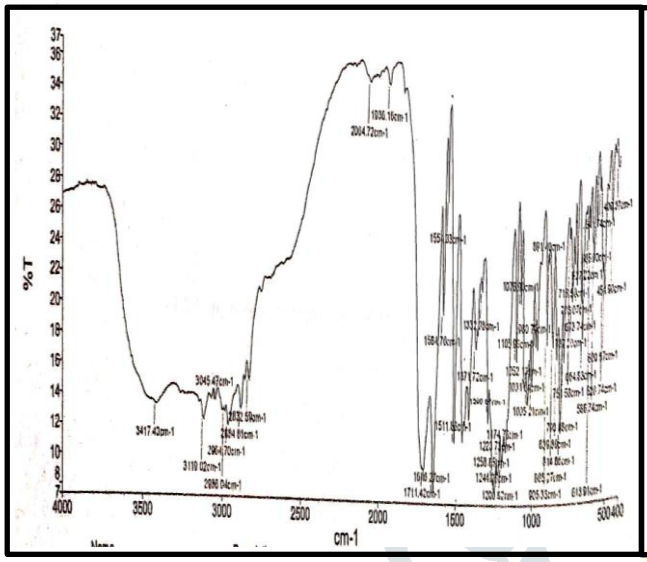

Fig 8.FTIR spectrum of Ketoconazole+ Avicel ph102

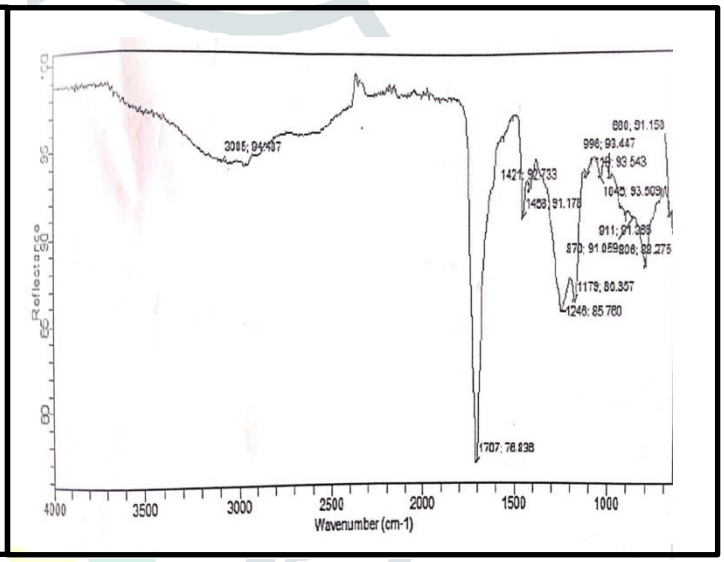

Fig 9. FTIR spectrum of Ketoconazole + PEG 400

Partition coefficient

As the experiment result reveal the observed log p value of drug matches with the standard given value. Hence the drug is lipophilic.

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Solubility

Solubility studies are carried of drug in different solvent and analyzing them spectrophotometrically.

TABLE NO.3. Partition coefficient

S.no.	Observed log p	Standard log p
1.	3.904	4.35
2.	4.326	4.35

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Solubility studies for the selection of non-volatile solvents

The solubility of ketoconazole was determined in various nonvolatile liquid vehicles such as Propylene glycol (PG), Polyethylene glycol (PEG 400), Tween 80, Polysorbate 80.From the results, it was observed that the solubility of drug in PEG-400 was higher

TABLE NO.4. Solubility

S.no.	Solvent	Concentration (µg/ml)	Solubility	Indication
1.	Phosphate buffer ph 6.8	10.303	Soluble	From 10 to 30
2.	Methanol	12.240	Soluble	From 10 to 30
3.	.1 N HCl	15.254	Soluble	From 10 to 30
4.	Ethanol	34.316	Sparingly soluble	From 30 to 100

when compared with other non-volatile liquid vehicles. It was observed that the drug is Soluble in Methanol, Phosphate buffer pH 6.8,.1 N HCl and Sparingly soluble in Ethanol.

TABLE NO.5. Solubility studies for the selection of non-volatile solvents

S.no.	Solvent	Concentration (µg/ml)	Solubility	Indication
1.	Peg-400	0.35425	Very soluble	Less than 1
2	Propylene glycol	1.3012	Freely soluble	From 1 to 10
3.	Polysorbate 80	2.5238	Freely soluble	From 1 to 10
4.	Tween 80	4.5472	Freely soluble	From 1 to 10

PRECOMPRESSIONAL EVALUATION OF POWDER BLEND

Powder flow is a critical character that might affect uniformity of the tablet weight. Therefore, the flow properties of the powder blend of all liquisolid formulations were determined in order to calculate that the amount of carrier and coating materials were required to maintain acceptable flow and compaction properties.

The powder blend of all formulations was evaluated for precompression parameters such as angle of repose, bulk density, true density, carr's index, Hausner's ratio and drug content.

TABLE NO. 6. PRECOMPRESSIONAL EVALUATION OF POWDER BLEND

Formulations	Angle of repose (mean±s.d.)	Bulk density (gm/ml) (mean±s.d.)	Tapped density (gm/ml) (mean± s.d.)	Carr's index (%) (mean±s.d)	Hausner's ratio (mean±s.d)
F1	24.13±1.83	0.261±0.045	0.252±0.02	11.29±0.86	1.068±0.02
F2	26.36±0.67	0.295±0.032	0.279±0.001	12.17±0.81	1.002±0.04
F3	23.12±1.23	0.596±0.09	0.461±0.00	10.04±0.26	1.102±0.01
F4	28.96±2.51	0.774±0.065	0.377±0.12	12.3±1.55	1.651±0.05
F5	25.15±1.81	0.354±0.074	0.669±0.09	11.26±0.78	1.325±0.03
F6	27.19±0.89	0.693±0.035	0.332±0.04	10.89±0.32	1.018±0.02
F7	24.61±2.13	0.846±0.068	0.771±0.01	11.6±0.78	1.325±0.03
F8	25.54±1.92	0.381±0.037	0.881±0.34	13.2±0.39	1.950±0.06
F9	29.01±2.06	0.795±0.061	0.921±0.04	10.05±0.67	1.425±0.09

Angle of Repose

The angle of repose is a characteristic of the internal friction or cohesion of the particles, the value will be low, if the powder is non-cohesive and high if the powder is cohesive. All the prepared formulations were in the ranges from 23.14° to 29.01° , which indicates the good flow properties of liquisolid powder.

Bulk density

Bulk density was used to measure the flow properties of the powder. The bulk density of the powder blend was in the range of 0.261 gm/ml to 0.846 gm/ml.

Tapped density

The tapped density of the powder blend was in the range of 0.252 gm/ml to 0.921 gm/ml.

Carr's Index (CI)

Determination of carr's index, the ratio of bulk and tapped density, was used to measure the flow property of all liquisolid formulations. The decrease the value of the CI% would indicate the better flow properties of the powder. The carr's index

of the all formulations was found to be in range of 10.04% to 13.2%. It was less than 25%, which indicates that the powder blend have required flow property for compression of tablets.

Hausner's Ratio

The Hausner's ratio of all the formulations was found to be in range of 1.002 to 1.950, which indicates better flow property of the powder blend.

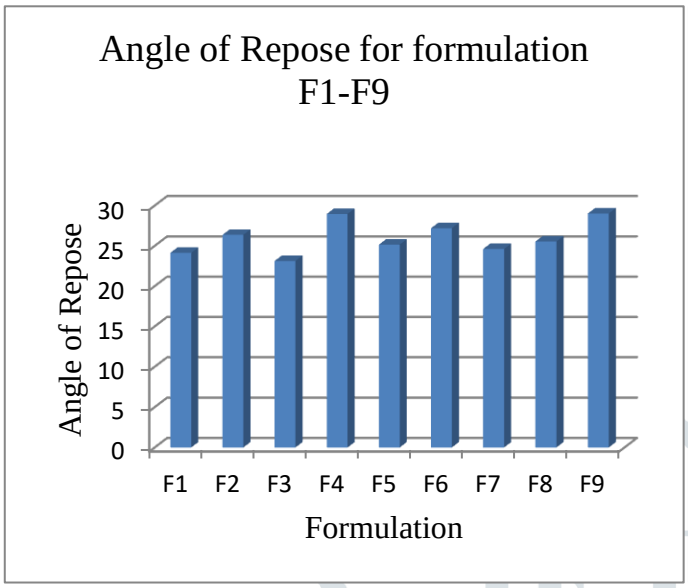


Fig 10. Angle of Repose for formulation F1-F9

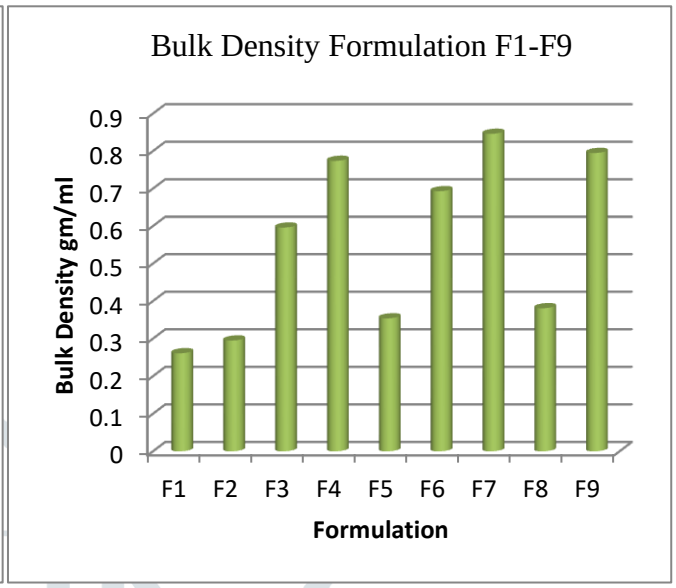


Fig 11. Bulk Density Formulation F1-F9

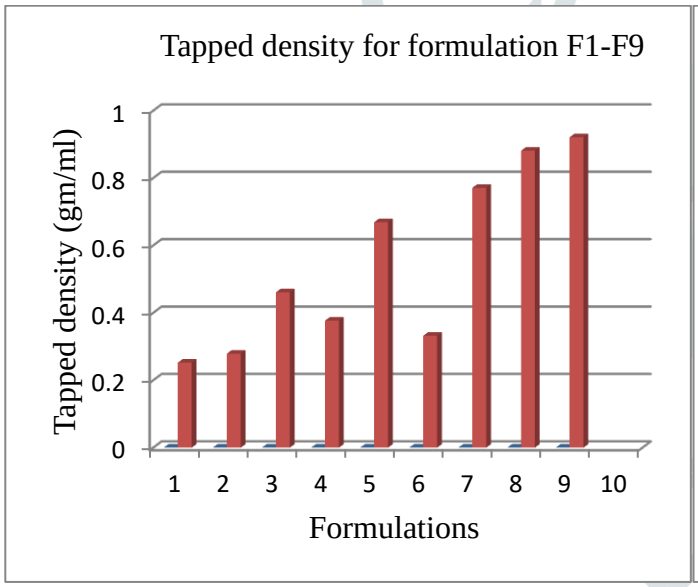


Fig 12. Tapped density for formulation F1-F9

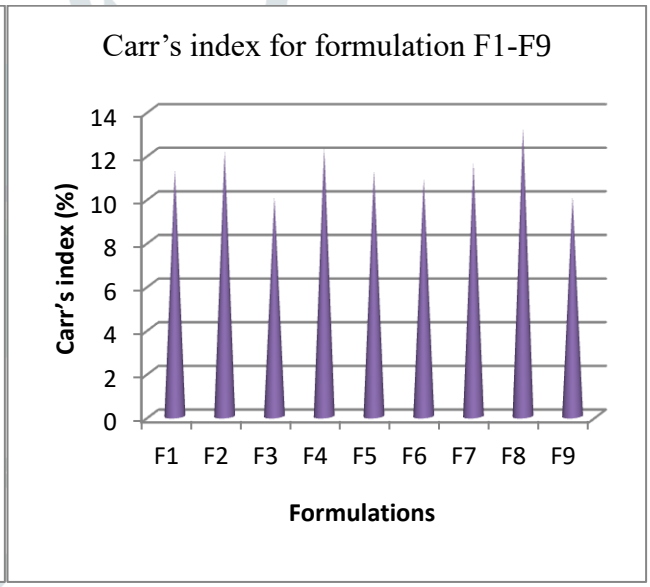


Fig 13. Carr's index for formulation F1-F9

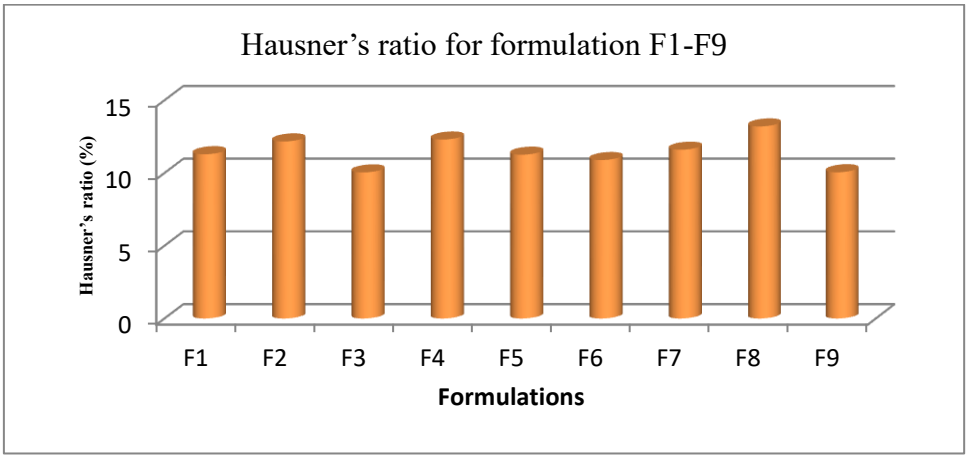


Fig 14: Hausner's ratio for formulation F1-F9

TABLE NO.7. FORMULATION OF ORODISPERSIBLE LIQUISOD TABLETS

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ketoconazole(mg)	100	100	100	100	100	100	100	100	100
Peg 400 (mg)	100	100	100	100	100	100	100	100	100
Excipient ratio	5	5	5	10	10	10	15	15	15
Loading factor;	0.804	0.804	0.804	0.67	0.67	0.67	0.574	0.574	0.574
Avicel ph102 (mg)	125	125	125	150	150	150	175	175	175
Aerosil 200 (mg)	25	25	25	15	15	15	11.66	11.66	11.66
Sd(mg) 1:1 1:2 1:3	10 - -	- 10 -	- - 10	10 - -	- 10 -	- - 10	10 - -	- 10 -	- - 10
Magnesium stearate(mg)	20	20	20	20	20	20	20	20	20
Talc(mg)	20	20	20	20	20	20	20	20	20
Flavour(mg)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Weight of tablet(mg)	405.5								

POST COMPRESSION PARAMETERS OF ORODISPERSIBLE LIQUISOLID COMPACTS TABLETS

Tablets of different formulations were evaluated for the post compressional parameters such as general appearance, weight variation, hardness, thickness, friability, disintegration time and drug content for tablets.

TABLE NO.8. Post compression parameters of orodispersible liquisolid compacts tablets

Formulations	Hardness k g/cm2 (mean± s.d.)	Friability %	Thickness mm (mean± s.d.)	% weight variation (mean± s.d.)	Drug content (%) (mean±s.d.)
F1	3.46±0.21	0.496	4.03±0.021	0.016±0.23	95.13
F2	3.31±0.01	0.423	4.02±0.015	0.042±0.45	96.22
F3	3.52±0.20	0.450	4.13±0.015	0.047±0.47	99.32
F4	4.22±0.25	0.592	4.11±0.004	0.021±0.52	97.15
F5	3.54±0.45	0.510	4.01±0.012	0.031±0.37	98.25
F6	3.41±0.35	0.487	4.06±0.007	0.044±0.15	98.85

F7	4.35±0.09	0.590	4.00±0.014	0.037±0.19	96.12
F8	3.56±0.21	0.521	4.02±0.032	0.032±0.47	98.31
F9	3.21±0.28	0.568	4.09±0.009	0.049±0.34	99.85

General appearance

The formulated tablets were white in colour, biconvex and round shape. All the tablets were elegant in appearance.

Thickness

The thickness of all the tablet formulations was used to determine the uniformity of size and shape of the tablets. All the prepared tablet formulations were measured by vernier caliper and were found to be in the range of 4.00 to 4.11 mm. The results indicated that all the formulations had uniform size and shape.

Hardness

Hardness of tablet was used to determine the resistance to withstand mechanical shakes of handling in manufacture and packing. All the prepared tablets were determined using Monsanto hardness tester. The hardness of all the formulations was found to be 3.21to 4.35 Kg/cm2, which indicates that all the tablet formulations had good mechanical strength.

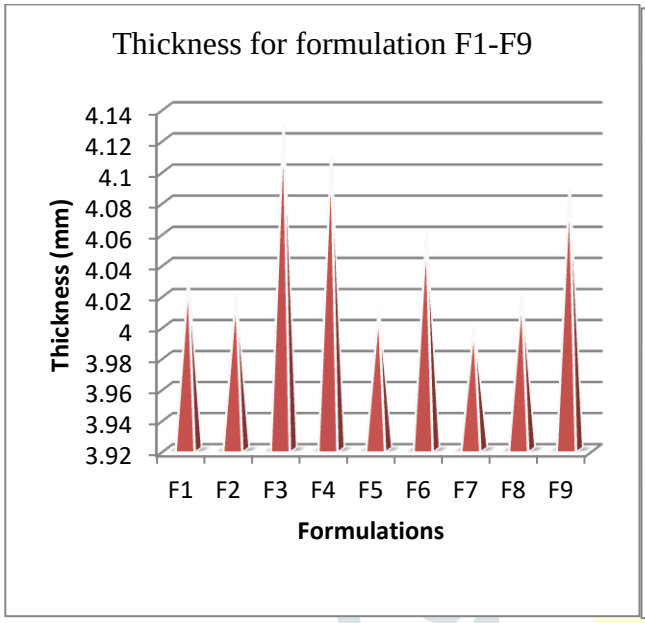


Fig 15. Thickness for formulation F1-F9

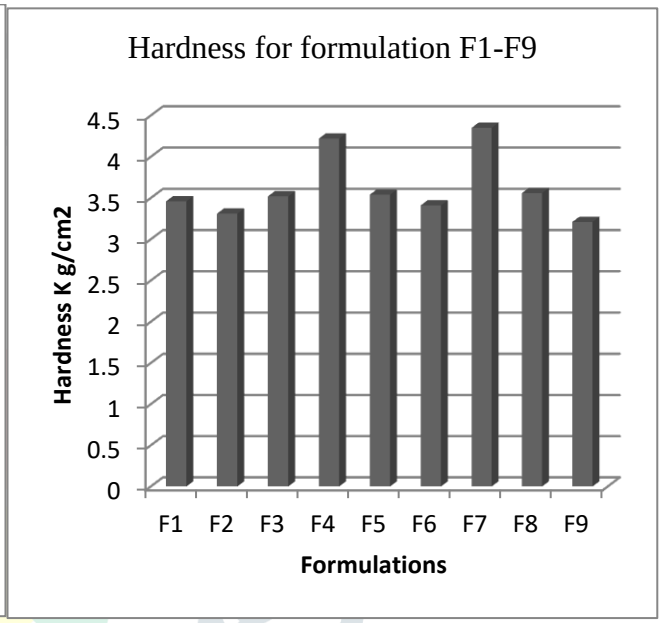


Fig 16. Hardness for formulation F1-F9

Weight variation

The weight was used to ensure the uniformity of the tablet in all formulations. All the formulation tablets passes the weight variations within the acceptable limits as per IP.

Friability test

The friability of tablets was determined using Roche friabilator and used to determine the mechanical strength of tablets. The percentage friability of all the tablet formulation was found to be in the range of 0.423 to 0.592 %. It was less then 1% the results indicated that all the tablets formulation had a good mechanical resistance of tablets.

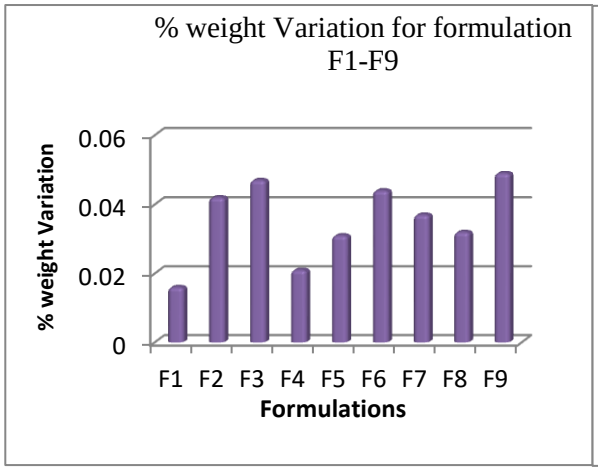


Fig 17. % weight Variation for formulation F1-F9

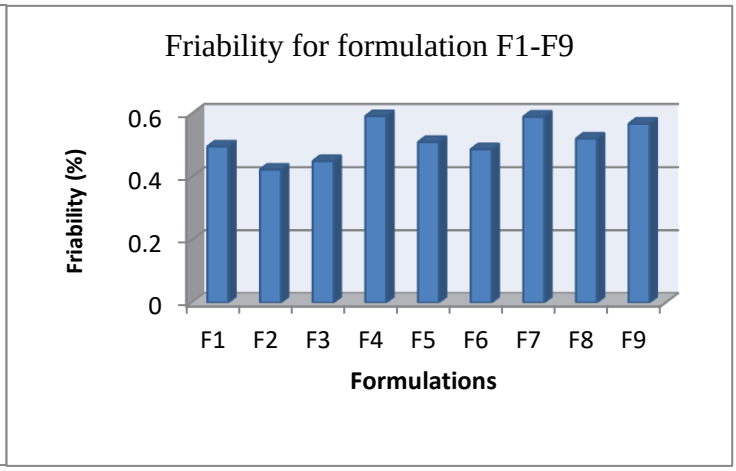


Fig 18. Friability for formulation F1-F9

Drug content

The drug content was used to determine the uniform amount of active ingredients presently in all the formulations. The drug content was found to be in the range of 95.13% to 99.85% which indicates all the formulations were within the acceptable limits as per IP (Limits not less then 85% and not more than 115%).

Disintegration test

The disintegration time of all the tablet formulations was determined using disintegration test apparatus. All the prepared tablet formulations were in between 49.32 sec to 88.78 sec. it was lesser then 2 minutes. Which indicates all the above post compressional evaluations were done for compressed tablets and they were within the limit which fulfill the pharmacopoeial requirement. In this study, the disintegrating effect of co-processed Superdisintegrants was studied by changing different ratio. The formulation F1 with 10 mg of co-processed Superdisintegrants in the ratio of 1:1 showed 88.78±1.02 sec and with 10 mg of co-processed Superdisintegrants in the ratio of 1:3 for formulation F3 showed lesser disintegration time of 49.32±2.53 sec. The results also suggested that co-processed Superdisintegrants showed faster disintegration time, due to the rapid uptake of water from the medium, swelling and burst effect.

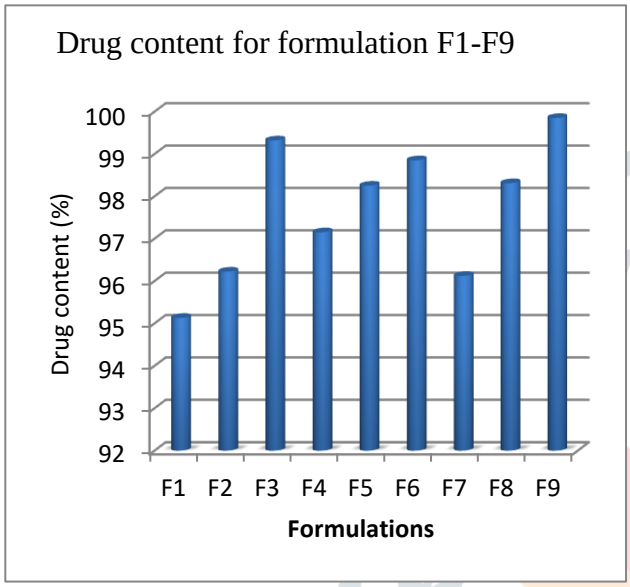


Fig 19. Drug content for formulation F1-F9

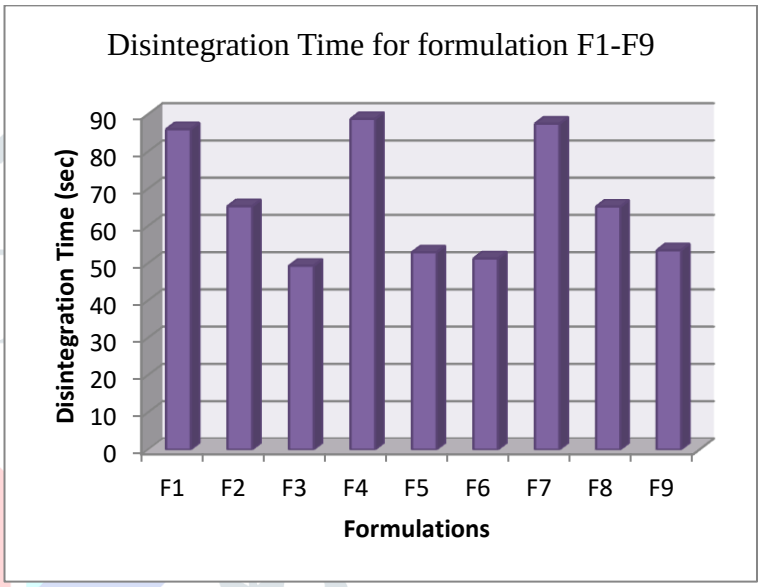


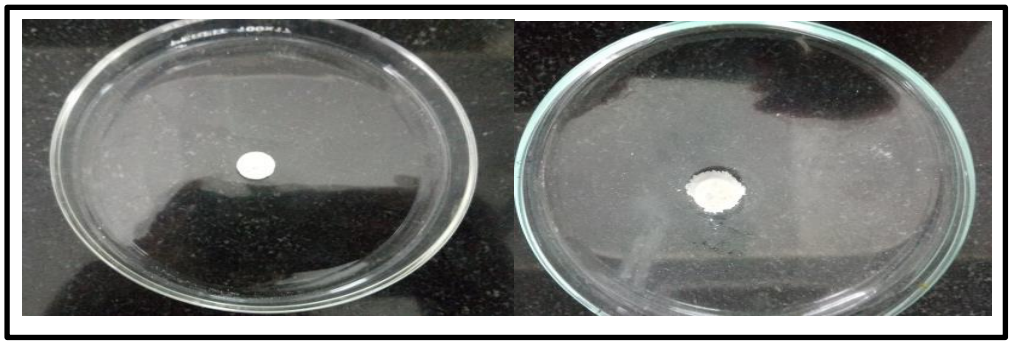
Fig 20. Disintegration Time for formulation F1-F9

TABLE NO. 9. Results of dispersion time, wetting time and water absorption ratio of orodispersible Ketoconazole tablet

Formulations	In-vitro dispersion time (sec) (mean± s.d.)	Disintegration time (sec) (mean± s.d.)	Wetting time (min) (mean± s.d.)	Water absorption ratio (%) (mean± s.d.)	Uniformity of dispersion
F1	84.12± 1.53	86.02± 2.00	2.59± 0.25	67.32± 0.87	Passes
F2	85.18 ±1.03	65.34± 1.52	2.53± 0.15	66.21± 0.94	Passes
F3	66.22± 1.52	51.30± 1.22	1.57± 0.57	65.59± 0.35	Passes
F4	61.40± 1.32	88.78± 1.02	2.58± 0.64	69.25± 1.20	Passes
F5	58.17± 1.57	52.96± 2.00	2.18± 0.16	73.58± 0.98	Passes
F6	49.28± 1.30	49.32± 2.53	1.59± 0.51	65.31± 1.72	Passes
F7	47.28± 1.58	87.51± 1.28	2.48± 0.20	66.21± 0.67	Passes
F8	69.22± 1.30	65.24± 1.34	2.15± 0.38	58.91± 1.08	Passes
F9	44.38± 1.85	53.52± 1.59	2.14± 0.34	72.54± 3.87	Passes

In-vitro dispersion time

The dispersion time was found to be in the range of in-vitro 44.38±1.85 - 85.18±1.03 sec



(a) (b)

Fig 21. In-vitro dispersion time at (a) 0 sec (b) at sec 44.38±1.85 of F9 formulation.

Wetting time

The wetting time of tablets was in the range of 1.57±0.57 - 2.59±0.25 min, which complies with the official specifications.

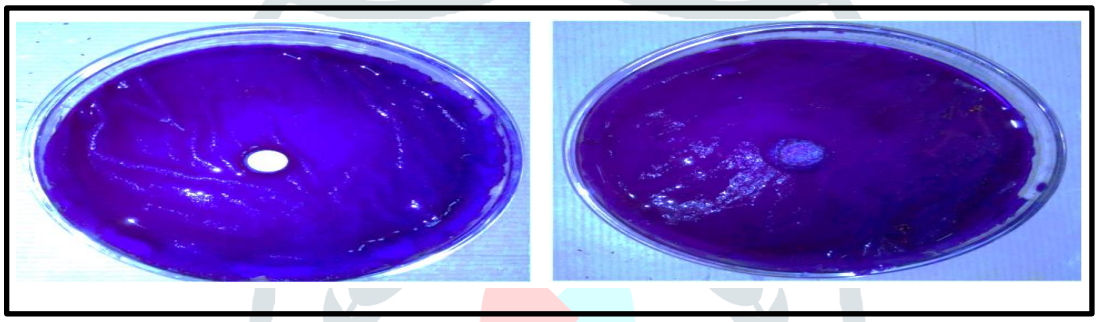


Fig 22. Wetting Time of F8 Formulation at (a) 0 min (b) at 1.57 min

Water absorption ratio

The water absorption ratio was found to be in the range 58.91±1.08 – 73.58±0.98 %

Uniformity of dispersion

The tablets were considered passing the test if no residue remained on the screen. All the formulation passes the Uniformity of dispersion test.

The dispersion time was found to be in the range of in-vitro 44.38±1.85 - 85.18±1.03 sec and shown in figure 4 (a) and figure 4 (b). The mean of the disintegration times for all investigated tablets was less than 2 min, which fulfil the pharmacopoeial requirement. The disintegration time was found to be in the range of 49.32±2.53 - 88.78±1.02 sec.

Invitro Release Profile Data Of Ketoconazole Liquisolid Compacts

TABLE NO. 10. Invitro Release Data Of Ketoconazole Liquisolid Compacts (F1-F5)

Time (min)	F1	F2	F3	F4	F5
0	0	0	0	0	0
5	11.21±0.8	16.28±1.6	35.21±1.20	12.25±0.9	26.71±0.11
10	15.54±1.3	25.24±0.95	41.65±1.12	18.95±0.42	35.81±0.20
15	22.16±0.9	29.53±0.04	47.29±1.05	24.35±0.23	44.22±0.31
20	29.27±1.10	33.47±1.07	51.35±0.7	35.37±1.23	48.79±0.35
25	33.42±0.75	39.31±1.00	60.21±0.3	41.98±1.62	56.25±0.23
30	45.63±0.4	45.68±0.23	68.54±0.9	49.21±1.14	62.54±0.24

35	55.21±1.32	56.20±0.84	75.14±1.32	56.24±1.05	71.32±0.41
40	64.11±1.02	68.54±0.9	82.07±0.9	64.33±0.76	80.64±0.86
45	70.35±0.98	76.85±1.12	90.57±1.1	70.63±0.42	86.65±0.72
50	76.12±0.17	80.31±0.7	99.21±1.6	77.32±0.31	93.23±0.54
55	81.03±0.45	88.42±1.09		84.21±0.41	99.54±0.23
60	87.54±0.67	96.32±1.3		89.54±0.20	

TABLE NO.11. Invitro Release Data Of Ketoconazole Liquisolid Compacts(F6-F9)

Time (min)	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0
5	40.55±0.15	13.98±0.59	23.06±0.47	39.23±0.54
10	51.56±1.06	20.83±1.03	30.50±0.31	47.95±0.23
15	60.21±0.01	26.45±1.07	37.14±0.20	55.32±0.43
20	67.20±0.42	35.04±0.42	46.14±0.41	60.84±0.35
25	77.54±1.03	42.17±1.06	52.32±0.12	68.25±0.23
30	85.52±0.59	51.54±1.05	66.25±0.20	75.57±0.20
35	91.35±1.62	60.25±0.76	72.83±0.86	81.23±0.57
40	99.65±0.61	67.41±0.57	80.65±0.20	91.14±0.64
45		71.74±0.29	85.81±0.89	99.86±0.98
50		77.74±0.59	93.54±0.23	
55		83.25±1.08	98.24±0.11	
60		89.47±0.42		

In vitro dissolution studies were carried out by USP type II method by using Phosphate buffer pH 7.4 as a medium. The samples were taken at an interval of 5 min absorbance was measured in UV spectrophotometer at 270 nm. three parameters such as effect of drug concentration in the liquid medication (ratio of drug and liquid vehicle) and effect of carrier/coating ratio (R value) and co-processed Superdisintegrants that would affect the drug dissolution rate in immediate release liquisolid tablets were investigated.

All Formulations were prepared with 1:1,(ratio of drug and Polyethylene glycol-400) and. Formulations F1, F2, F3, were prepared with 1:1,(ratio of MCC & Aerosil 200) Formulations F4, F5, F6 were prepared with 1:2 (ratio of MCC & Aerosil 200) Formulations F7, F8, F9, were prepared with 1:3 (ratio of MCC & Aerosil 200)
Formulations F1, F4, F7, were prepared with 1:1,(ratio of =Co-processed Superdisintegrants (crospovidone: croscarmellose sodium) showed the cumulative % of drug release 87.54%,89.54%,89.47% in 60 min respectively.
Formulations F2, F5, F8 were prepared with 1:2 ,(ratio of =Co-processed Superdisintegrants (crospovidone: croscarmellose sodium) showed the cumulative % of drug release 88.42%,99.54%,97.24% in 55 min respectively.
Formulations F3, F6, F9, were prepared with 1:3 ,(ratio of =Co-processed Superdisintegrants (crospovidone: croscarmellose sodium) showed the cumulative % of drug release 99.21%,in 50 min,99.65% in 40 min,,99.86% in 45 min.
The formulation which showed highest release among all the formulations was formulation 6.Among the nine formulations F6 has the maximum dissolution rate. It shows 51.56% percentage drug release in the first 10min and 99.65% release 40min. From within the above results it is clear that the increase in the amount of co-processed superdisintegrants, increased in the dissolution rate of the drug. It is because of increased aqueous solubility, and increased wetting property of the drug. The percentage of drug release of F1 – F9 shows 87.5%, 96.32%, 99.21%, 89.54%, 93.54%, 96.69%,89.47%,90.78%,98.71% respectively. Among the different formulations, F6 contains the co-processed superdisintegrants in the ratio of 1:3 and excipient ratio of R=10 and Liquid load factor of Lf=0.67 achieved 60% of drug release within 15 mins. These results suggests that the co-processed superdisintegrants in the ratio of 1:3 and excipient ratio of R=10 have faster disintegrating and dissolution effect.

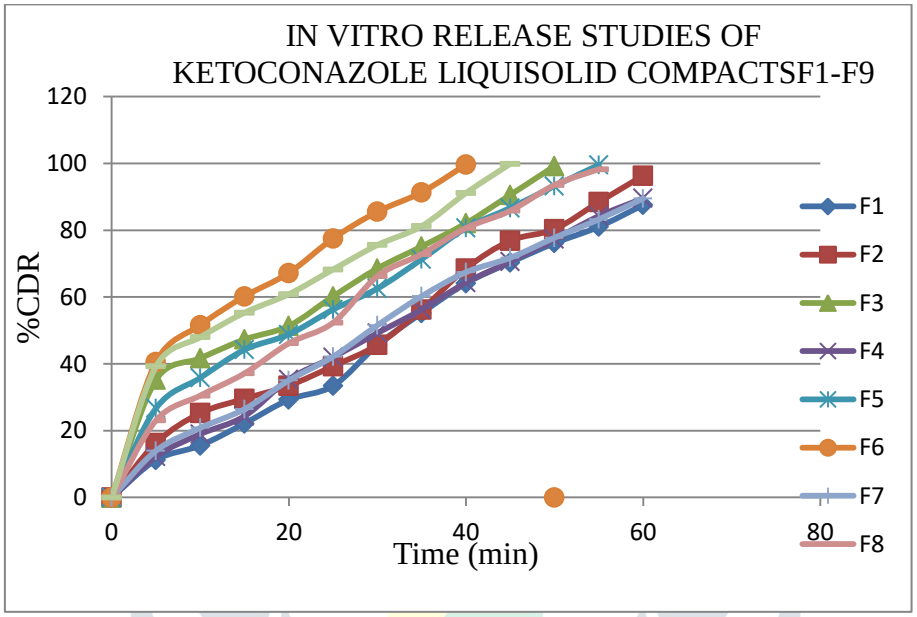


Fig 23. IN VITRO RELEASE STUDIES OF KETOCONAZOLE LIQUISOLID COMPACTS(F1-F9)

DRUG RELEASE KINETICS WITH MODEL FITTING

In vitro release data obtained for the formulations F1 to F9 shows release kinetics of ketoconazole liquisolid compact. The cumulative percentage drug release data obtained were fitted to zero order, first order Higuchi and Peppas Korsmeyer equations to understand the mechanism of drug release from the ketoconazole liquisolid compact. The coefficient of determination indicated that the release data was best fitted with zero order kinetics and Peppas Korsmeyer explains the diffusion controlled release mechanism.The diffusion exponent 'n' values were found to be in the range of 0.4 to 0.8 for the ketoconazole liquisolid compact indicating Fickian diffusion.

TABLE NO. 12. REGRESSION COEFFICIENT(R^2) VALUES OF DIFFERENT KINETIC MODELS AND DIFFUSION EXPONENT (n) OF PEPPAS MODEL FOR KITOCONAZOLE COMPACTS

Formulation	Zero order (r^2)	First order (r^2)	Higuchi matrix (r^2)	Hixson crowel (r^2)	Peppas plot		Best fit model	Mechanism of release
					R^2	N		
F1	0.9931	0.9442	0.9214	0.9753	0.9792	0.8986	Zero order	Anomalous transport
F2	0.9741	0.8969	0.9314	0.9767	0.9862	0.7400	Peppas korsmeyer	Anomalous transport
F3	0.9395	0.7147	0.9022	0.8913	0.9417	0.4582	Peppas korsmeyer	Fickian diffusion

								(higuchi matrix)
F4	0.9963	0.9387	0.9173	0.9786	0.9930	0.8364	Zero order	Anomalous transport
F5	0.9676	0.7188	0.9813	0.9116	0.9813	0.5586	Peppas korsmeyer	Anomalous transport
F6	0.9008	0.7314	0.9223	0.9247	0.9873	0.4338	Peppas korsmeyer	Fickian diffusion (higuchi matrix)
F7	0.9914	0.9526	0.9162	0.9857	0.9903	0.7872	Zero order	Anomalous transport
F8	0.9795	0.8494	0.9070	0.9557	0.9794	0.6449	Zero order	Anomalous transport
F9	0.9073	0.6141	0.9136	0.8618	0.9669	0.4182	Peppas korsmeyer	Fickian diffusion (higuchi matrix)

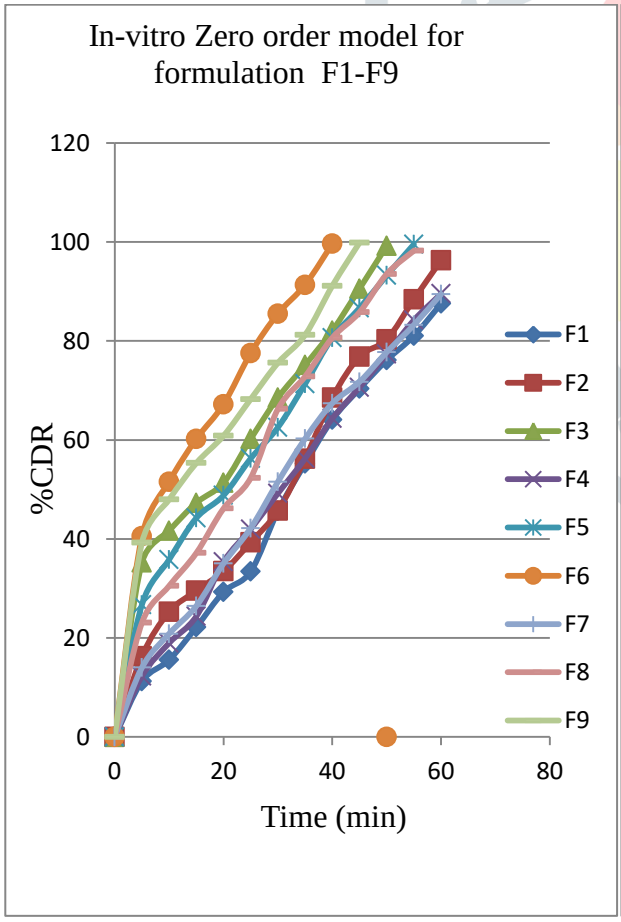


Fig 24. ZERO ORDER RELEASE KINETIC STUDIES OF ORODISPERSIBLE LIQUISOLID COMPACTS Of KETOCONAZOLE (F1-F9)

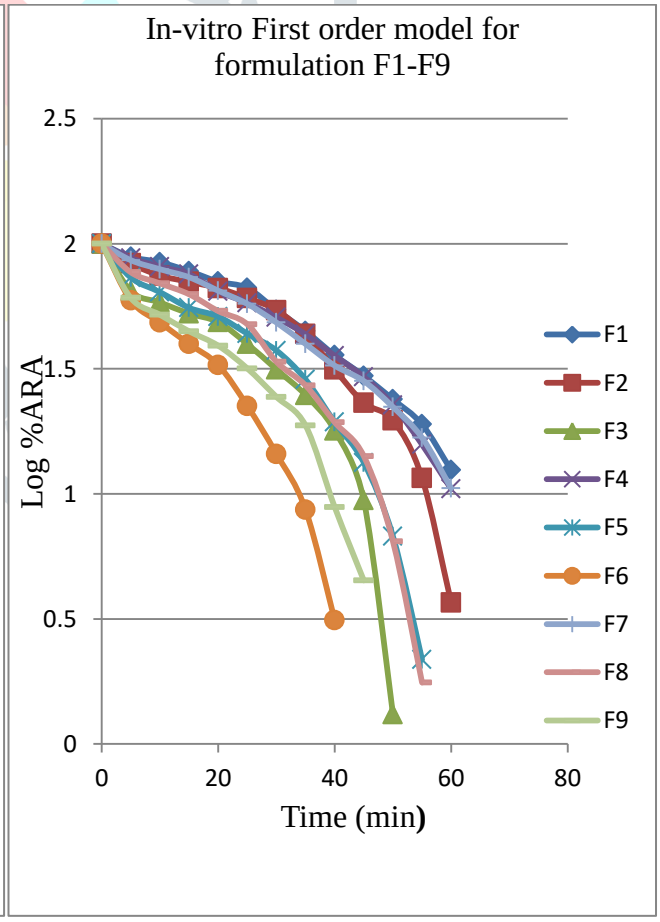


Fig 25. FIRST ORDER RELEASE KINETIC STUDIES OF ORODISPERSIBLE LIQUISOLID COMPACTS OF KETOCONAZOLE (F1-F9)

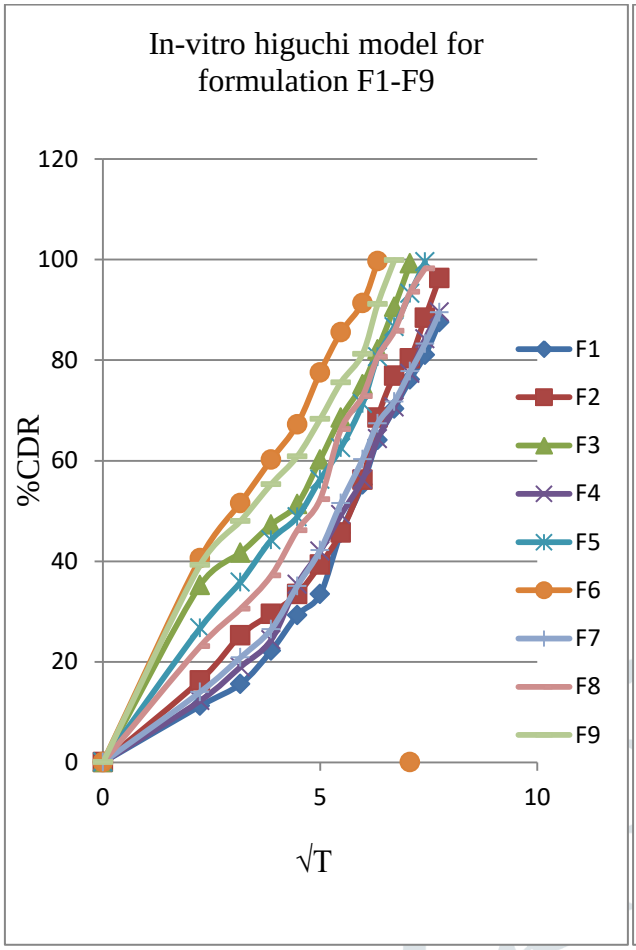


Fig 26. IN-VITRO HIGUCHI MODEL KINETIC STUDIES OF ORODISPERSIBLE LIQUISOLID COMPACTS OF KETOCONAZOLE (F1-F9)

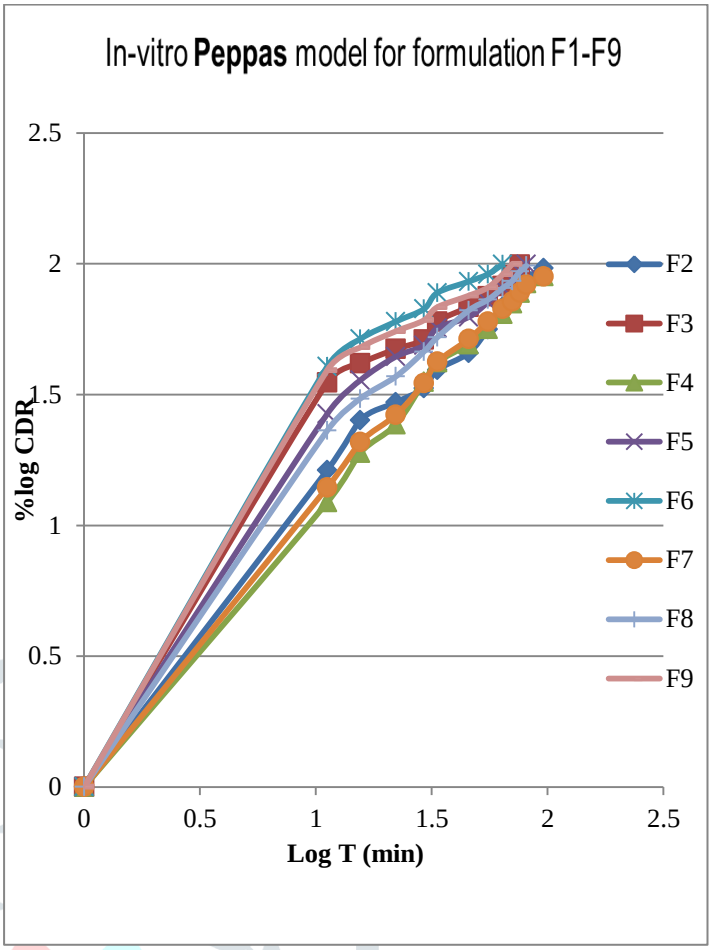


Fig 27. PEPPAS ORDER RELEASE KINETIC STUDIES OF ORODISPERSIBLE LIQUISOLID COMPACTS OF KETOCONAZOLE (F1-F9)

CONCLUSION

Solubility and dissolution are the major factors that affect the bioavailability and in vivo performance of the drug. Moreover, based on literature, most current drugs have high lipophilicity and poor aqueous solubility resulting in poor bioavailability. Liquisolid technique has been used successfully to produce a tablet dosage form of ketoconazole with faster dissolution rate than the regular tablet.

It was concluded that the ODTs can be successfully prepared using LS technology and adding co-processed superdisintegrants to the formulation in order to improve disintegration and dissolution rate of poorly water soluble drugs such as Ketoconazole. The tablets prepared with showed co-processed superdisintegrants highest dissolution rate. This may be attributed to rapid uptake of water with vigorous swelling ability of co-processed superdisintegrants. Hence, the combined effect of liquisolid compact technique and inclusion of different ratio of co-processed superdisintegrants is useful in enhancement of dissolution rate of Ketoconazole.. It can be said that liquisolid technique with co-processed superdisintegrants promising strategy in improving dissolution of insoluble drugs and formulating immediate release solid dosage forms. As the liquisolid technology uses similar production processes as followed to develop conventional tablets, this technology aims to improve the release rate of poorly water-soluble drugs via a simple and cost effective method to positively improve patient compliance.

Conflict of interest

The authors have no conflict of Interest

REFERENCES

1. Kansara, H., Panola, R. and Mishra, A., 2015. Techniques used to enhance bioavailability of BCS class II drugs: a review. International Journal of Drug Development and Research, 7(1), pp.82-93.
2. Patel, J.N., Rathod, D.M., Patel, N.A. and Modasiya, M.K., 2012. Techniques to improve the solubility of poorly soluble drugs. International Journal of Pharmacy & Life Sciences, 3(2), pp1459-1469.
3. Humberstone, A.J. and Charman, W.N., 1997. Lipid-based vehicles for the oral delivery of poorly water soluble drugs. Advanced drug delivery reviews, 25(1), pp.103-128
4. Vasconcelos, T., Sarmento, B. and Costa, P., 2007. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug discovery today, 12(23), pp.1068-1075.
5. Sultana, S., Halder, S., Kabir, A.L. and Rouf, A.S.S., 2015. Effect of solubility enhancers on the release of Carbamazepine from Hydrophilic Polymer based matrix tablet. Dhaka University Journal of Pharmaceutical Sciences, 13(2), pp.167-173.
6. Xingwang Zhang 1 ID, Huijie Xing 2, Yue Zhao 2 and Zhiguo Ma 1; "Pharmaceutical Dispersion Techniques for Dissolution and Bioavailability Enhancement of Poorly Water-Soluble Drugs", Pharmaceutics 2018, 10, 74;1-33.

7. S.Spireas,S.Sadu,andR.Grover,"Invitroevaluationofhydrocortisoneliquisolidtablets,"JournalofPharmaceuticalSciences, vol.87,no.7,pp.867–872,1998.
8. Satyajit Panda, R. Varaprasad, K. Priyanka, Ranjit P. Swain;"Liquisolid Technique: A Novel Approach For Dosage Form Design". Issn- 0975-7058 Vol 9, Issue 3, 2017;8-14.
9. Dokoumetzidis A., & Macheras P (2006); A century of dissolution research: from Noyes and Whitney to the biopharmaceutics classification system; International journal of pharmaceutics; 321(1-2); 1-11.
10. Surti N, Patel DS, Pipaliya RM. Liquisolid tablets for dissolution enhancement of a hypolipidemic drug. Indian J Pharm Sci 2015;77:290-8.
11. Meena K, Sneha M. A review on pioneering technique-liquisolid compact and applications. Res J Pharm Biol Chem Sci 2015;6:220-7
12. Gubbi S.R., Jarag R (2009); "Liquisolid Technique for enhancement of dissolution properties of Bromhexine Hydrochloride"; Research J. Pharm. And Tech; 2(2); 382-386.
13. Seager H. (1998). "Drug-delivery products and Zydis fast dissolving dosage form." Journal of Pharmacy and Pharmacology 50(4): 375-382.
14. https://pubchem.ncbi.nlm.nih.gov/compound/Ketoconazole
15. Shah, A., Shah, S., Patel, V., & Potdar, A. (2012). Nanonization: A Dissolution Enhancement Approach for BCS Class II Drugs. Drug Development and Delivery, 12(1), 48-52
16. Arora SC, Sharma PK, Raghuveer I et al. Development, characterization and solubility study of solid dispersion of cefixime trihydrate by solvent evaporation method. International journal of drug development and research., 2010; 2(2): 424-230.
17. Martindale(2009) The complete drug reference, 36th edition, RPS Publication, pp 1324.
18. Knox, C., Law, V., Jewison, T., Liu, P., Ly, S., Frolkis, A., Pon, A., Banco, K., Mak, C., Neveu, V. and Djoumbou, Y., 2010. DrugBank 3.0: a comprehensive resource for 'omics' research on drugs. Nucleic acids research, 39(1), pp.D1035-D1041.
19. Jagdish Rathi, Mithun Bhowmick, Rahul Sharma, Sagar Panse, Rupal Pandit, Sachin Gupta. Development and In-vitro characterization of floating drug delivery system of ketoconazole. Journal of Drug Delivery and Therapeutics 2019; 9(1):22-29
20. Spireas S. (2002). "Liquisolid systems and methods of preparing same." United States Patent 6,423,339 B1.
21. Indian Pharmacopoeia. 1996. 4th Ed. Vol. I: Controller of Publications, Ministry of Health & Family Welfare, Govt. of India, Delhi, pp 511-13.
22. Dobetti M. 2011. Fast Melting Tablets: Developments and - Technologies. Pharmaceutical Technology and Drug Delivery. 44 50.
23. Parmar K, Patel J, Sheth N. Fabrication and characterization of liquisolid compacts of Embelin for dissolution enhancement. J Pharm Investig 2014;44:391-8
24. Lachman L, Lieberman H, Kanig J. 1987. The theory and practice of industrial pharmacy, 3rd Edn, Varghese Publishing House, Mumbai, p 297.
25. Kanagathara N, Shenbagarajan P, Esther JC, Thirunavukkarasu C. 2011. Fourier Transform Infrared Spectroscopic Investigation on Nifedipine. International Journal of Pharma and Bio Sciences, 1(2):52-56.
26. Patel P, Tanwar YS, Jaimin M, Amit P. 2013. Orodispersible Tablet of Proton Pump Inhibitor Drugs: A Review. Journal of Pharmaceutical Science and Bioscientific Research, 3(2):2271 -3681.
27. Sreenivas SA, Gadad AP. 2006. Formulation and evaluation of Ondancetron HCl directly compressed mouth disintegrating tablets. Indian Drugs, 43(1):35- 38.
28. Altememy DR, Altememy JJ. Formulation and evaluation of meloxicam liquisolid compact. Int J Pharm Pharm Sci 2014;6:453-63.
29. Rajesh M, Palanichamy S, Ravi KN, Jeganath S, Thangathirupathi A. 2011. Formulation development and evaluation of Piroxicam orodispersible tablets using different superdisintegrants. Der Pharmacia Lettre, 3(4):155-62.
30. Munke AP, Nagarsenker MS. 2004. Triamterene β-cyclodextrin complexes: Preparation, characterization and In vivo evaluation. American Association of Pharmaceutical Scientists: PharmSciTech, (5):1-9.
31. Bayrak Z, Tas C, Tasdemir U, Erol H, Ozkan CK, Savaser A, et al. Formulation of zolmitriptan sublingual tablets prepared by direct compression with different polymers: In vitro and in vivo evaluation. Eur J Pharm Biopharm 2011;78:499-505
32. Patel RP, Patel H, Baria AH. Formulation and evaluation of carbopol gel containing liposome of Ketoconazole. Int J Drug Del Technol 2009;1:42-5.
33. Kopp S. Stability testing of pharmaceutical products in a global environment. Regulatory Affairs J 2006;16:291-4.
34. Pradeep C, Venugopalaiah H, Praveen P, Gnanaprakash K, Gobinath M. 2013. Liquisolid Systems – An Emerging Strategy For Solubilization & Dissolution Rate Enhancement of BCS Class-II Drugs. International Journal of Pharmacy Review & Research, 3(2):56-66.