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IMMEDIATE AND MUCOADHESIVE SUSTAINED RELEASE COMPACTS OF ITRACONAZOLE USING LIQUISOLID TECHNOLOGY

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Abstract

Liquisolid technique was used as a novel approach to develop immediate release and sustained release formulations. Itraconazole was selected as a model drug for this approach. The objective of the study was to increase the dissolution of Itraconazole by formulating it into immediate release compacts and to increase the bioavailability of itraconazole by formulating it into mucoadhesive sustain release compacts. Propylene glycol, PEG 400, PEG 600, Tween 80 and span 80 were used as nonvolatile liquid vehicles. In immediate release formulations Avicel pH 200, Aerosil 200 sodium starch glycolate were used. HPMC K4M, Carbopol 940 and Chitosan were selected as carrier polymer and Aerosil 200 was selected as coating material for mucoadhesive sustained release compacts. It was observed that the percentage drug release for immediate release compact S-8 (optimized) was found to be 100% within 45 mins, whereas marketed capsule (SPORONOX) reported 100% drug release after 90 mins. The mucoadhesive sustained release liquisolid compact MHP-4(HPMC K4M as polymer/carrier) reported sustained activity for 8 h following zero order kinetics with greater mucoadhesion property.

Keywords: Itraconazole, liquisolid compacts, PEG 600, Aerosil 200, Avicel pH 102, Mucoadhesive liquisolid compacts, Propylene glycol, HPMC K4M, Carbopol 940 and Chitosan.

1. Introduction

A liquisolid system is a powdered form of liquid drug formulated by converting liquid lipophilic drug or drug suspension or solution of water insoluble drug in suitable nonvolatile solvent system into dry looking, non adherent, free flowing and readily compressible powdered mixtures by blending with selected carrier and coating materials. Generally, in the

liquisolid systems the drug might be in a solid dosage form, which is held within the powder substrate in a solution form. Therefore, due to significant increase in the wetting properties and surface area available for dissolution, liquisolid compacts of water insoluble drugs can enhance the drug release properties and consequently improve bioavailability.[1]

The drug in the form of a solution in a suitable non-volatile liquid vehicle is incorporated into the porous carrier material which is inert. Generally water-miscible organic solvent systems with high boiling point such as propylene glycol, liquid polyethylene glycols, or glycerin are selected as liquid vehicles. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles [2]. Thus, an apparently dry, free flowing, and compressible powder is obtained. Usually, microcrystalline cellulose is used as carrier material and amorphous silicon dioxide (colloidal silica) as coating material to form a liquisolid system.

Various excipients such as lubricants and disintegrants (immediate release) or matrix forming materials (sustained release) may be added to the liquisolid system to produce liquisolid compacts.

The drug solution or drug suspension can be prepared by dissolving the poorly water soluble drugs in the inert nonvolatile solvents forming liquisolid compacts results in enhanced drug release due to an increased surface area of drug available for release, an increased aqueous solubility of the drug, and an improved wettability of the drug particles. Accordingly, this improved drug release may result in a higher drug absorption in the gastrointestinal tract and thus, an improved oral bioavailability [3].

Itraconazole is a broad-spectrum triazole agent available for the treatment of histoplasmosis, blastomycosis, onychomycosis and amphotericin B-refractory aspergillosis. Itraconazole is highly effective in vitro against Candida albicans and other Candida species, including many resistant to fluconazole. Itraconazole is ionized only at a low pH, such as gastric juice and as a result on oral administration, the gastric acidity is required for adequate dissolution. The bioavailability of itraconalzole is known to be increased after a meal in comparison to the fasting state.

Itraconazole belongs to Biopharmaceutics Classification Systems Class II drugs categorized with low water solubility and high permeability. Because of poor dissolution in the gastrointestinal tract, its oral administration was involved with large variations in bioavailability; therefore enhancing the dissolution rate of itraconazole is an important task for its formulation development.[4,5]. The primary objective of formulating a mucoadhesive dosage form is to provide intimate contact of the dosage form with the gastric mucosa and to increase the residence time of the dosage form at the gastric

mucosa to prolong drug action resulting in increase of the bioavailability of itraconazole (absorption for itraconazole is high in gastric environment).

This study is aimed to formulate different liquisolid dosage forms of immediate release compacts using super disintegrants like sodium starch glycolate and mucoadhesive sustained release compacts using mucoadhesive polymers such as Carbopol 940, HPMC K4M & Chitosan. Primarily the drug was made to solubilize in the nonvolatile solvent and was mixed with carrier material to absorb the liquid containing drug and later mixed with coating material (adsorbent) such as Aerosil 200 to form a free flowing powder. This blend was compressed into circular compacts.

2. Materials and Methods

2.1. Materials

Itraconazole was a kind gift from Hetero drugs ltd (Hyderabad), Avicel pH 102 was procured from Zhaveri pharmakhem pvt ltd (Mumbai), Aerosil200, Propylene glycol, PEG400, PEG 600, Tween 20, Tween 80, Span 80, Sodium starch glycolate, HPMC K4M, Carbopol 940, Chitosan, Sodium tri poly phosphate and Sodium saccharine were procured from SD fine chemicals Mumbai. All the chemicals and solvents used in this study are of anlalytical grade.

2.2 Solubility studies

Solubility studies were carried out using the conventional Shake flask method. To select the suitable non-volatile solvent, solubility studies of itraconazole were carried out in various solvents, i.e. PEG 200, PEG 400, glycerin, tween 20, tween 80, span 80 and Propylene glycol. Saturated solutions were prepared by adding excess drug to the above solvents individually. The contents were kept on orbital shaker (Eltek orbital shaker) for 48h at room temperature. The resultant solutions were filtered through a Millipore whatmann filter (0.45 µm), diluted with 0.1N HCl and analysed by UV-spectrophotometer (Lab India) at a wavelength of 254 nm against blank sample.

2.3 Measurement of Angle of Slide.

This experiment was designed to measure the flowable liquid retention potential (Ø) value for the excipients required to formulate a liquisolid system. In this study, Avicel PH 102(carrier material, $Ø_{Ca}$), Aerosil (coating material, $Ø_{Co}$) and the optimum liquid load factor (Lf) were calculated.

The **Ø-value** of a powder is the maximum amount of given nonvolatile liquid that can be retained inside powder bulk (w/w) while maintaining acceptable flowability.

L_f is the mass ratio (w/w) of the liquid medication to the carrier powder in the liquisolid formulation.

Powder admixtures containing 5 g of carrier and coating material separately with increasing quantity of nonvolatile liquid vehicle were mixed using a mortar and pestle. Each admixture was then placed on a shiny metal plate; the plate was then tilted until the admixture slides. The angle formed between the plate and the horizontal surface, at which admixture slides were measured as angle of slide (θ).The flowable liquid retention potential was calculated using the following equation:

$$Ø\text{-Value} = \frac{\text{Weight of nonvolatile liquid}}{\text{Weight of carrier or coat}} \quad \ldots\ldots\ldots (1)$$

Each admixture has specific Ø-value which was determined and plotted against respective measured angle of slide for all nonvolatile liquid vehicles. The Ø-value that corresponds to an angle of slide of $33^0$was reported to represent the flowable liquid retention potentials of powder admixtures [8].

2.4 Application of Mathematical Model for Design of Liquisolid Compacts:

To achieve good flow and compressibility of liquisolid systems, a mathematical model designed by Spireas et al[1] was used in the present work. In this study, propylene glycol was used as liquid vehicle, Micro crystalline cellulose phosphate (Avicel PH102), colloidal silicon dioxide (Aerosil 200), were used as carrier and coating material respectively. Concentration of the drug in propylene glycol was taken as 100%, 90%, 80%, 70% and carrier to coating material ratios were selected, ranging from 5-20.

Liquid Loading Factor (L_f): It is defined as the maximum weight of liquid that can be retained per unit weight of powder material in order to produce acceptable liquid powder admixture.

$$Lf = Ø_{CA} + Ø_{CO}\,(1/R) \quad \ldots\ldots\ldots (2)$$

$Ø_{CA}$- Flowable liquid retention potential of the carrier material

$Ø_{CO}$ - Flowable liquid retention potential of the coating material

R - Excipient ratio

Liquid loading factor is also defined as ratio of weight of liquid medication (W) to the weight of carrier material (Q)

$$Lf = W/Q \quad \ldots\ldots\ldots (3)$$

Excipient ratio "R" of a powder is defined as the ratio of the weight of the carrier material (Q) to the weight of the coating material (q), present in formulation.

$$R = Q/q \quad \ldots\ldots\ldots (4)$$

2.5. Preparation of Powder Blend for Liquisolid Tablets.

Immediate release: Several itraconazole liquisolid formulations were prepared at different drug concentrations of 70%(w/w) to 100% (w/w) in liquid vehicles using PEG 600 as nonvolatile solvent each formulation was prepared using Avicel PH 102 as carrier and Aerosil 200 as coating material at carrier/coat ratio of 5, 10, 15 and 20 which has ben shown in Table 1.

The appropriate amount of carrier and coating materials used for each formulation depends upon L_f of that formulation. The drug was made to dissolve or suspended in respective nonvolatile liquid by heating at 50^0 C and later sonicated for 15 mins. To this liquid medication, the calculated amount of the carrier was added by continuous mixing in the mortar. Then, coating material was carefully added and mixed until mortar contents start to look dry. In the last stage of the preparation, a 5% (w/w) sodium starch glycolate and 5 % (w/w) sodium saccharine was added to all formulations for immediate release.

All the formulations were subjected for flow properties. Based on flow properties the formulations are optimized and were compacted into tablets using 12 station rotary compression machine (Rimek) using 12mm circular flat punches plain on both sides.

Table-1: Various formulations of Itraconazole immediate release liquisolid compacts.

FORMULATION CODE	DRUG conc (%w/w)	Excipient ratio (R)	Liquid load factor L_f	Q= W/L_f (mg)	q= Q/R. (mg)	Unit dose (mg)
S-1	70%	5	0.634	111.9	22.3	215.4
S-2	70%	10	0.319	222.5	22.2	331.4
S-3	70%	15	0.214	331.7	22.1	446.0
S-4	70%	20	0.161	440.9	22.0	560.0
S-5	80%	5	0.634	97.7	19.5	188.1
S-6	80%	10	0.319	194.3	19.4	289.4
S-7	80%	15	0.124	289.7	19.3	389.5
S-8	80%	20	0.161	385.0	19.2	489.5
S-9	90%	5	0.634	86.7	17.3	166.9

S-10	90%	10	0.319	172.4	17.2	256.8
S-11	90%	15	0.214	257.0	17.1	345.8
S-12	90%	20	0.161	341.6	17.0	434.2
S-13	100%	5	0.634	78.8	15.7	151.7
S-14	100%	10	0.319	156.7	15.6	233.4
S-15	100%	15	0.214	233.6	15.4	313.9
S-16	100%	20	0.161	310.5	15.0	394.2

All formulations contain 5% (w/w) of SSG

Mucoadhesive Sustained release liquisolid compacts:

Mucoadhesive compacts using Carbopol 940 (MCA), Chitosan (MCH) and HPMC K4M (MHP) were prepared at different drug concentrations ranging from 50%(w/w) to 70% (w/w) in Propylene glycol as nonvolatile liquid and Aerosil 200 was used as coating material at carrier/coat ratio of 5, 10 and 15 to sustain the drug release. About 2% (w/w) of Sodium tripoly phosphate was added as a cross linking agent to increase the hardness of the MCH tablets. Table 2 represents various formulations of Itraconazole mucoadhesive liquisolid compacts

Flow properties such as Carr's index, angle of repose, and Hausner's ratio were studied and the formulations were selected for further studies. The tablets were compressed using 12 station rotary compression machine (Rimek) using 12mm circular flat punches plain on both sides.

Table-2: Various formulations of Itraconazole mucoadhesive liquisolid compacts.

FORMULATION CODE	DRUG conc (%w/w)	Excipient ratio (R)	Liquid load factor L_f	$Q= W/L_f$ (mg)	q= Q/R. (mg)	Unit dose (mg)
MCA-1	50%	5	0.667	153	30.5	255.5
MCA -2	50%	10	0.335	307.4	30.7	440.1
MCA -3	50%	15	0.225	453.3	30.2	585.5
MCA -4	60%	5	0.667	123	24.6	249.6
MCA -5	60%	10	0.335	244.7	24.7	371.4
MCA -6	60%	15	0.225	360	24	486

MCA -7	70%	5	0.667	106.4	21.2	229.6
MCA -8	70%	10	0.335	211.9	21.2	304
MCA-9	70%	15	0.225	315.5	21	438.5
MCH -1	50%	5	0.679	150.2	30	287.8
MCH -2	50%	10	0.347	294	29.4	406.3
MCH -3	50%	15	0.237	430.3	28.6	468
MCH -4	60%	5	0.679	120.7	24.1	251.7
MCH -5	60%	10	0.347	236.3	23.6	347.7
MCH -6	60%	15	0.237	430.3	28.6	468
MCH -7	70%	5	0.679	104.5	20.9	200.3
MCH-8	70%	10	0.347	204.6	20.4	301.9
MCH-9	70%	15	0.237	299.5	19.9	398.2
MHP-1	50%	5	0.667	153	30.5	255.5
MHP-2	50%	10	0.335	307.4	30.7	440.1
MHP-3	50%	15	0.225	453.3	30.2	585.5
MHP-4	60%	5	0.667	123	24.6	249.6
MHP-5	60%	10	0.335	244.7	24.7	371.4
MHP-6	60%	15	0.225	360	24	486
MHP-7	70%	5	0.667	106.4	21.2	229.6
MHP-8	70%	10	0.335	211.9	21.2	304
MHP-9	70%	15	0.225	315.5	21	438.5

2.6 Differential Scanning Calorimetry:

Differential Scanning Calorimetry study was carried out using calibrated Shimadzu DSC-60 (Shimadzu, Kyoto, Japan). DSC thermograms of pure drug itraconazole, and powder mixture for optimized liquisolid preparations were obtained. DSC aluminium cells were used as sample holder, and blank DSC aluminium cell was used as reference. 2-3mg sample

was used for analysis. Thermograms were recorded over the range of 20 ^{0} C–300 ^{0}C at a constant rate of 20 ^{0}C per minute under nitrogen purge at 20 mL/min.

2.7 X-Ray Diffraction Studies:

X ray diffractograms of ITZ, and LS formulation were recorded by using "PAN analytical X'pert pro". The cross section of the samples were exposed to X-Ray radiation with scanning range of

0-80 θ.

Post compression evaluation:

The compressed tablets were evaluated for weight variation, hardness (Monsanto hardness tester) and friability (Roche friabilator).

2.8 *In-vitro* Disintegration Time.

The disintegration time of the tablets was measured in 0.1N HCl (37 ± 2^{0}C) using disintegration test apparatus (Electrolab, India). Six tablets from each formulation were tested for the disintegration time.

2.9 Swelling index.

Agar (5% w/v) was dissolved in hot water, transferred into Petri plates and allowed to solidify. Mucoadhesive tablets were then placed on the surface of the agar and incubated at 37^{0}C until constant weight is observed. At the end of test, percentage moisture absorption was calculated using the following formula.

$$\% \text{ Swelling index} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

2.10 *Ex-vivo* mucoadhesive strength

Ex vivo mucoadhesive strength of itraconazole mucoadhesive tablets was measured by using modified physical balance method. Fresh goat stomach membrane was obtained from male/female goat with an average weight of 65 ± 6 kg, from the local slaughterhouse and stored in pH1.2 buffer and the experiment was performed within 3 h of procurement of goat mucosa. The goat stomach mucosa was fixed to an open mouth vial containing the buffer with a cyanoacrylate adhesive and placed in a beaker; then pH 1.2 buffer (0.1N HCl) was added into the beaker up to the upper surface of the goat stomach mucosa to maintain mucosal viability during the experiment. Then the tablet was attached to the upper clamp of the apparatus and the beaker was raised slowly to establish contact between goat stomach mucosa and the tablet.

Later water was added into the beaker which was placed on other side of the balance using a burette at a constant rate. The weight required to detach the mucoadhesive tablet from the mucosal surface was measured which gives the value of mucoadhesive strength in gm (total weight of water in beaker). Experiments were carried out triplicate and the average values were recorded.

2.11 Content Uniformity.

Five tablets were powdered, and 50mg equivalent weight of itraconazole was accurately weighed and transferred into a 100mL volumetric flask. Initially, the tablet powder was made soluble in few ml of methanol and shaken for 10min. Then, the volume was made up to 100mL using 0.1N Hcl. The solution in the volumetric flask was filtered, diluted suitably, and analyzed spectrophotometrically at 254 nm using UV-visible double-beam spectrophotometer (Lab India).

2.12 *In-vitro* Dissolution Studies.

The in vitro dissolution studies of the tablets was performed using USP type II apparatus (electro lab) at 37^0C $\pm 0.5^0$C using 0.1N Hcl (900 ml) as a dissolution medium at 50 rpm. At the predetermined time intervals, 5mL samples were withdrawn and replaced with fresh dissolution media. Withdrawn samples were filtered through whatmnn filter paper (0.45μm), diluted, and assayed at 254nm using a double-beam spectrophotometer (Lab India). Cumulative percentage drug release was calculated using an equation obtained from a calibration curve.

2.13 Stability studies

The stability studies were carried out for optimized formulation of itraconazole immediate release (S-8) and mucoadhesive sustained release liquisolid compact (MHP-4). The formulations were stored at 40º ± 2ºC/75% ± 5% RH for 3 months (Climatic zone IV condition for accelerated testing) to assess their stability.

The protocol of stability studies was in compliance with the ICH guidelines for stability testing intended for the global market. After intervals of 30, 60, and 90 days, samples were withdrawn and re-tested for drug content, drug release studies and hardness.

3. Results and Discussion

3.1 Solubility Studies of Itraconazole.

Solubility data of drug Itraconazole in various liquid vehicles is shown in Table 3. Itraconazole reported more solubility in PEG 600 than other vehicles. Therefore PEG 600 was used as non volatile solvent for immediate release compacts.

Whereas Itraconazole reported lower solubility in propylene glycol compared to other cosolvents used in the present study (Table 3). Propylene glycol was therefore used as a non-volatile solvent in the preparation of liquisolid systems for further studies to sustain the drug release.

Table-3: Solubility studies.

S.NO	LIQUID	SOLUBLE CONC (mg/ml)
01	Water	0.001 ±0.0002
02	Propylene glycol	0.83 ± 0.005
03	PEG 400	1.47 ± 0.007
04	PEG 600	35.40. ± 0.005
05	Tween 20	2.10 ± 0.004
06	Tween 80	2.80 ± 0.003
07	Span 80	1.05 ± 0.01

Each value represents mean ± SD (n=3)

3.2 Angle of slide measurement: Based on the formula, Ǿ values were calculated and reported in Table 4. According to the ratio of the carrier/coating material (R), $Ǿ_{CA}$, $Ǿ_{CO}$ values, Lf were calculated (From Eq 2). From the liquid vehicle concentration (W), Liquid loading factor (Lf) values, appropriate quantities of carrier and coating materials were calculated by using eq. 3, and eq. 4 respectively.

Table-4: Angle of Slide.

S.No	Ingredient	Nonvolatile solvent	Ǿ value
01	Microcrystalline cellulose	PEG 600	0.004
02	Aerosil	PEG 600	3.15
03	Carbopol 940	Propylene glycol	0.004,
04	Chitosan	Propylene glycol	0.004

05	HPMC K4M	Propylene glycol	0.016
06	Aerosil	Propylene glycol	3.31

3.2 Precompression Studies

3.2.1 Flow properties of Itraconazole immediate release compact blend:

The flow properties of all the formulations were assessed. The optimized formulations were selected based on the angle of repose representing good flow properties with an angle $<33^0$. Table (5) represents the flow properties of itraconazole immediate release tablets.

The precompression studies of immediate release compacts reported that S-3, S-8, S-10 and S-15 were having good flow properties with an angle of repose $<33^0$and hence these formulations were selected for further studies by subjecting them for compression.

Table-5: Precompression studies of Itraconazole immediate release formulations.

Formulation Code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index	Hausners ratio	Angle of repose (θ)
S-3	0.42 ±0.02	0.49 ±0.05	14.23 ±0.02	1.16 ±0.06	25.86 ±0.04
S-8	0.39 ±0.03	0.51 ±0.02	21.54 ±0.04	1.30 ±0.02	26.58 ±0.03
S-10	0.35 ±0.02	0.50 ±0.03	30.06 ±0.02	1.40 ±0.02	30.95 ±0.02
S-15	0.34 ±0.02	0.41 ±0.02	17.05 ±0.04	1.20 ±0.02	32.68 ±0.04

3.2.2. Flow properties of Itraconazole mucoadhesive sustain release compact blend:

Table (6) represents the flow properties of itraconazole mucoadhesive sustain release dosage form. The formulation code represents the type of polymer used such as, MCA represents Mucoadhesive compact using Carbopol 940 as polymer, MCH represents Mucoadhesive compact using Chitosan as polymer and MHP represents Mucoadhesive compact using HPMC K4M as polymer.

From Table 6 it is evident that the precompression studies of mucoadhesive sustain release compact blends of MCA-4, MCA-8, MCH-4, MCH-7, MHP-4, MHP-8 were having good flow properties with an angle of repose $<33^0$and hence these formulations were selected for further studies by subjecting them for compression.

Table-6: **Precompression studies of mucoadhesive sustained release formulations.**

Formulation Code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index	Hausners ratio	Angle of repose (θ)
MCA-4	0.27 ±0.03	0.41 ±0.02	34.1 ±0.02	1.51 ±0.02	29
MCA-8	0.30 ±0.02	0.48 ±0.01	37.5 ±0.2	1.60 ±0.02	27
MCH-4	0.27 ±0.02	0.37 ±0.04	27.0 ±0.02	1.37 ±0.02	29
MCH-7	0.24 ±0.02	0.32 ±0.02	25.0 ±0.02	1.33 ±0.02	27
MHP-4	0.26 ±0.03	0.41 ±0.02	36.5 ±0.02	1.57 ±0.02	28
MHP-8	0.29 ±0.02	0.47 ±0.01	38.2 ±0.2	1.62 ±0.02	29

Each value represents mean ± SD (n=3)

3.3 Post compression evaluation

3.3.1. Immediate release:

The formulations with good flow properties were subjected for compression and evaluated for weight variation, hardness, disintegration time, friability and content uniformity and reported in Table 7. From the results it can be stated that S-8 reported optimum hardness with lower friability and 100% content uniformity.

Table-7: Post compression evalution of Itraconazole immediate release liquisolid compacts.

Formulation code	Weight variation (gm)	Hardness ($kg/cm^{2)}$	Disintegration time (secs)	Friability (%)	Content uniformity(%)
S-3	446.22 ± 0.10	2.8 ± 0.15	90±2	0.88 ±0.10	98.64 ± 0.10
S-8	**499.65 ± 0.10**	**4.5 ± 0.15**	**100**±3	**0.20 ±0.10**	**100.22 ± 0.10**
S-10	258.05 ± 0.10	2.5 ± 0.10	90±2	0.76 ±0.20	99.46 ± 0.20
S-15	320.15 ± 0.10	3.0 ± 0.10	90±2	0.36 ±0.25	94.25 ± 0.20

Each value represents mean ± SD (n=3)

3.3.2. Mucoadhesive sustained release:

The formulations with good flow properties (MCA-4, MCA-8, MCH-4, MCH-7, MHP-4, MHP-8) were subjected for compression and evaluated for weight variation, hardness, friability, content uniformity, swelling index and *Ex-vivo* mucoadhesive strength and reported in Table 8.

Table-8: Post compression evalution of mucoadhesive sustained release liquisolid compacts.

Formulation code	Weight variation (gm)	Hardness ($kg/cm^{2)}$	Friability (%)	Content uniformity (%)	Swelling index (%)	Ex-vivo mucoadhesive strength (gm)
MCA-4	250.00 ± 0.15	5.05± 0.15	0.20 ±0.18	98.63 ±0.05	40±2	17.9±0.20
MCA-8	305.05 ± 0.10	5.55 ± 0.10	0.25±0.05	100.05 ±0.01	34.8±1.5	12.96±0.10
MCH-4	300.50± 0.15	4.54 ± 0.14	0.38±0.10	97.43 ±0.05	80±2	6.65±0.10
MCH-7	200.15 ± 0.10	4.55± 0.15	0.37 ±0.10	96.25 ±0.02	75±1	4.40±0.20
MHP-4	**250.00 ± 0.10**	**4.90± 0.15**	**0.20 ±0.10**	**100.20 ±0.05**	**36±2**	**18.96±0.10**
MHP-8	305.05 ± 0.10	5.00 ± 0.10	0.20±0.05	98.90 ±0.10	26±2	16.95±15

From the results it can be stated that MHP-4(HPMC K4M as polymer/carrier) reported optimum hardness with lower friability, 100% content uniformity and greater mucoadhesive strength.

3.3.3 Dissolution studies of immediate release liquisolid compacts:

The compressed formulations and marketed formulation (SPORONOX) were subjected to *in-vitro* drug release studies.

Type of apparatus: Paddle type

Media: 0.1N Hcl

Volume: 900 ml

Temperature: 37^0 C ±0.5^0 C

RPM: 50 rpm

Absorption maximum: 254nm

Analyzed using:

UV-visible double-beam spectrophotometer (Lab India)

The data of Comparison of Cumulative % drug release between prepared Itraconazole immediate liquisolid tablets and SPORONOX (Brand capsule) was reported in Table 9.

Table-9: Comparison of Cumulative % drug release between prepared Itraconazole immediate liquisolid tablet and SPORONOX (Brand capsule).

TIME (mins)	S-3	S-8	S-10	S-15	SPORONOX
0	0.00	0.00	0.00	0.00	0.00
5	33.31 ±0.12	33.32 ±0.10	22.23 ±0.13	22.2 5±0.17	25.42±0.12
10	48.23 ±0.15	67.12 ±0.12	50.24 ±0.15	38.64 ±0.12	40.25±0.13
15	68.72 ±0.12	84.84 ±0.16	72.75 ±0.12	56.82 ±0.15	51.35±0.11
30	75.85 ± 0.15	91.12 ±0.11	84.52 ±0.16	69.92 ±0.15	59.62±0.15
45	84.32±0.17	100.15 ±0.12	91.74±0.12	72.5±0.12	72.06±0.12
60	89.20±0.09		97.05± 0.09	81.54±0.13	85.45±0.15
75	93.25 ±0.10		100.03 ±0.15	89.21 ±0.11	97.68 ±0.14
90	97.03 ±0.09			94.58 ±0.12	100.03 ±0.11

The powder excipient ratio (*R*) also plays an important role in drug release rate, from the results it can be concluded that there was a direct relationship between the powder excipient ratio (*R)* and the release of drug from liquisolid tablets, when *R* value increases, the release rate will also increase. i.e., liquisolid tablets of *R* =20 had higher drug release than liquisolid tablets of lower R values. So, from above data that S-8 was selected as optimized formulation which is having the higher R value. The drug release of S-8 was higher which when compared to that of the other selected formulations. Hence S-8 was selected as optimized formulation and compared with marketed capsule (SPORONOX). The optimized Itraconazole immediate release liquisolid compact was compared with the marketed formulation of itraconazole (Sporonox). From the

Fig 1, it can be seen that the release rate of liquisolid compact was markedly higher than that of the marketed capsule. It was observed that the percentage drug release for immediate release compact S-8 (optimized) was found to be 100% within 45 mins, whereas marketed capsule (SPORONOX) reported 100% drug release after 90 mins

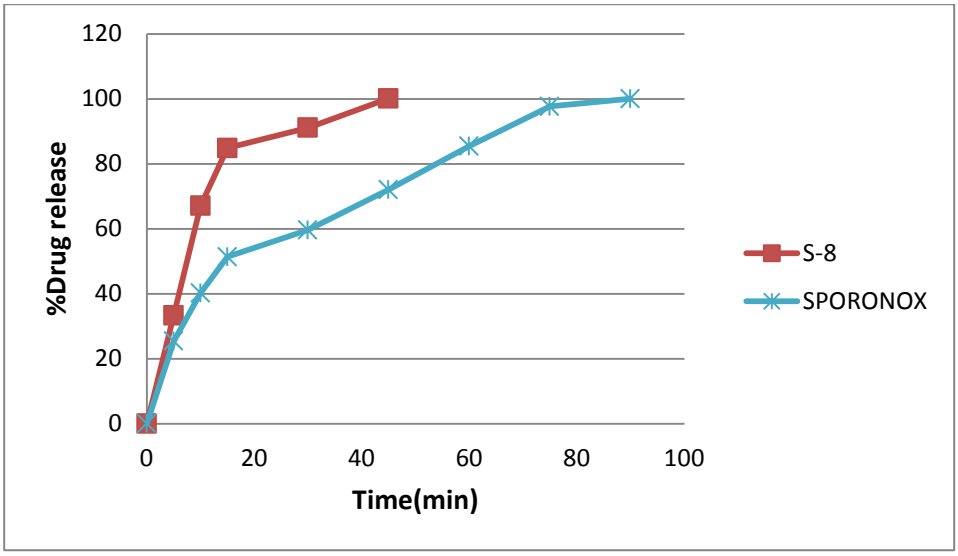


Fig-1: Comparison of % cumulative drug release vs time profile of optimized liquisolid immediate release formulation (S-8) and Sporonox (marketed capsule).

3.3.4 *In-vitro* drug release studies of sustained release liquisolid compacts:

The compressed formulations of sustained release compacts (MCA-4, MCA-8, MCH-4, MCH-7, MHP-4, MHP-8) were subjected to *in-vitro* drug release studies and reported in Table 10.

Table-10: *In-vitro* drug release of Itraconazole Mucoadhesive sustained release compacts.

TIME (hrs)	MCA-4	MCA-8	MCH-4	MCH-7	MHP-4	MHP-8
0	0.00	0.00	0.00	0.00	0.00	0.00
2	19.7± 0.15	21.7± 0.15	11.3±0.15	13.3±0.15	13.8±0.11	18.7± 0.15
4	41.20±0.10	44.9±0.10	35.9±0.10	38.9±0.11	44.5±0.15	40.9±0.10
6	72.40±0.13	76.12±0.13	67.10±0.20	69.10±0.14	79.0±0.20	76.12±0.10
8	91.20±.09	96.8±0.09	76.1±0.20	79.1±0.15	100.0±0.10	94.80±0.09

From the results it can be reported that formulation MHP-4 sustained the drug release for 8 hours. These results were later fitted for drug release kinetics.

3.3.4.1 Drug release kinetics:

The drug release data of optimized mucoadhesive sustain release liquisolid compact (MHP-4) was fitted to zero order, first order, Higuchi and Korsmeyer-Peppas model to study the kinetics of drug release and the results were tabulated in Table 11.

Table-11: Drug release kinetics of optimized formulation (MHP-4):

Time (Hr)	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remaining	log time	log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
2	21.8	78.2	1.414	1.893	0.301	1.338	21.8	4.276	0.366
4	46.5	53.5	2.000	1.728	0.602	1.667	24.7	3.768	0.874
6	75.6	24.4	2.449	1.387	0.778	1.879	29.1	2.900	1.742
8	100	0	2.828	0.000	0.903	2.000	24.4	0.000	4.642

Using the results, different graphs were plotted to predict the type of drug release that the optimized formulation.

From the graphs plotted, the regression coefficient was calculated for all types of drug release kinetics. And from Table 12 it was reported that the optimized formulation (MHP-4) follows zero order kinetics with R^2 value of 0.997. From this it can be stated that the drug release from the mucoadhesive compact is constant by maintaining the bioavailability.

Table-12: Regression analysis of optimized formulation (MHP-4).

Type of Drug release kinetics	Graph Plotted against	R^2 value
Zero order	Time Vs cumulative % drug released	0.997
First order	Time Vs log Cumulative % drug remaining	0.760
Higuchi	Square root of time Vs cumulative % drug released	0.892
Korsmeyer-peppas	Log time Vs log Cumulative % drug remaining	0.955
Hixsoncrowell equation	Cube root of (Wo) - Cube root of(Wt)	0.820

3.5 Powder X-ray diffraction analysis:

X-ray diffraction patterns revealed that pure itraconazole was in crystalline state (Fig 3), as it showed sharp distinct peaks notably at 2θ diffraction angles of 21.35^0, 37.49^o. The reflections (specific peaks) corresponding to the pure drug were not found in the optimized formulation diffractogram. This indicates that the crystallinity of the drug in the formulation was decreased thus facilitating the conversion of crystalline to amorphous form and thereby enhanced drug dissolution.

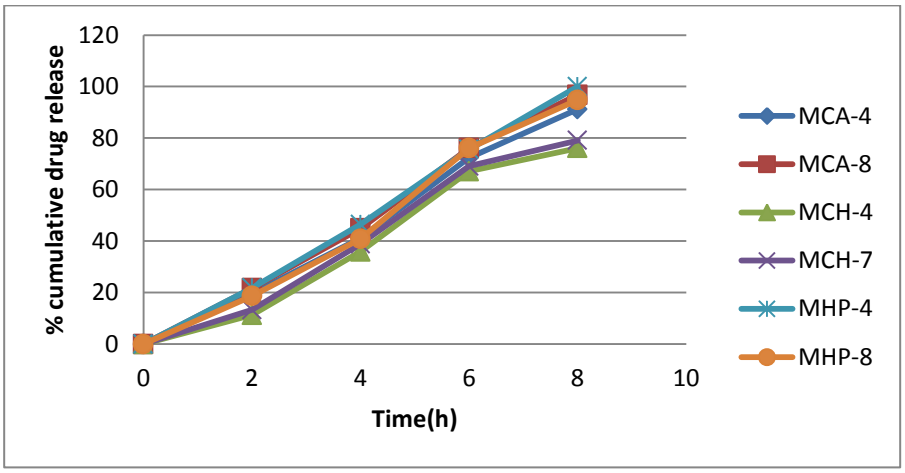
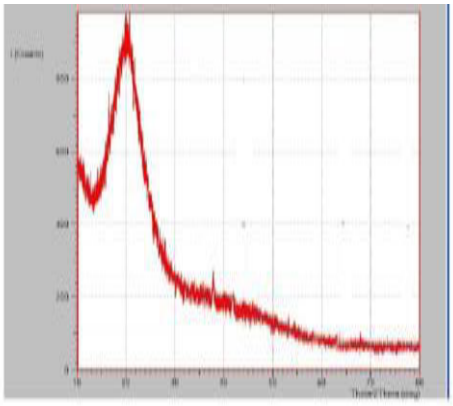
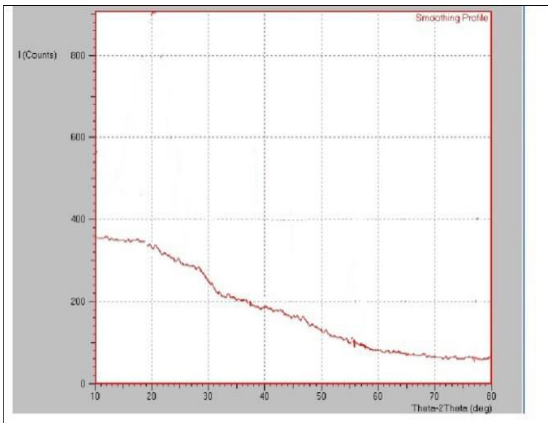


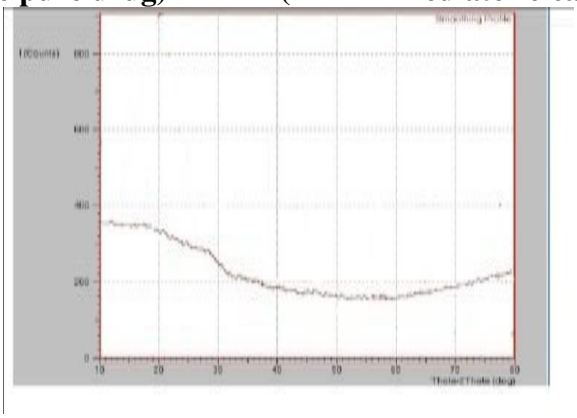
Fig: 2 cumulative % drug release vs time profile of mucoadhesive sustained release liquisolid formulations.



(Itraconazole pure drug)

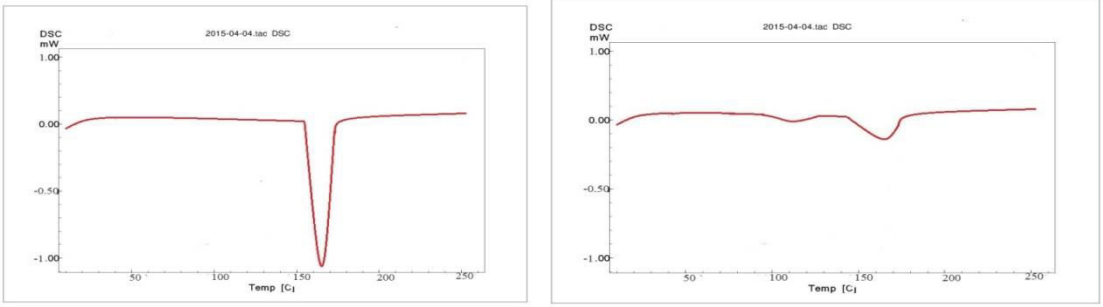


(ITZ immediate release compact)

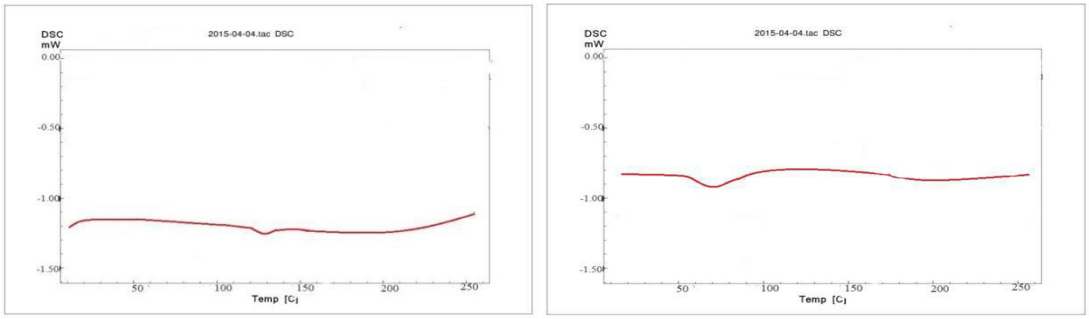


(ITZ sustained release LSD compact).

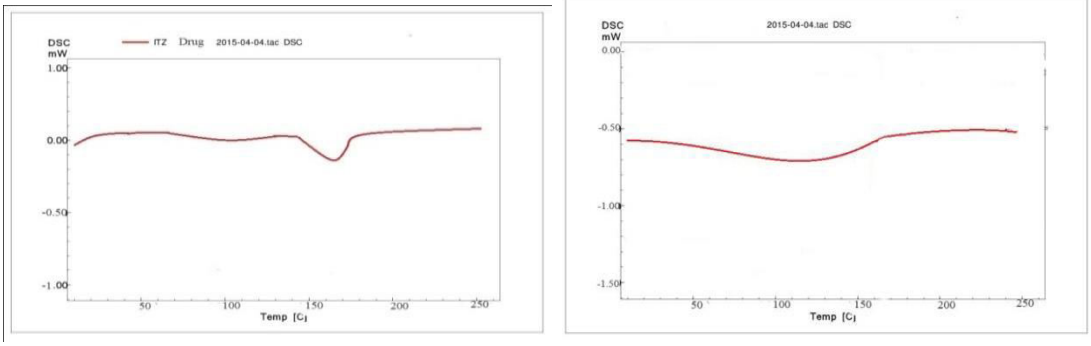
Fig:3 XRD profile of ITZ pure drug and immediate and sustained release liquisolid compacts.



(a) Itraconazole pure drug **(b) ITZ immediate release liquisolid compact**



(c) Aerosil 200 **(d) Avicel pH 102**



(e) Sustained release liquisolid compact **(f) HPMC K4M**

Fig 4: DSC profile of Itraconazole pure drug, immediate and mucoadhesive sustained release liquisolid compact (optimized formulations) and their excipients.

3.6 Differential Scanning Calorimeter:

The thermogram of pure itraconazole showed a sharp endothermic peak at 166^{o}C (T onset = 160.16^{0} C; ΔH=64.4 J/gm), indicating the crystalline nature of the drug. Avicel PH 102 showed a peak at 2θ diffraction angles of 37.61^{o}. Whereas HPMC K4M and Aerosil 200 displayed broad peaks at 110.36^{0} C & 120.7^{0} C. DSC thermogram of both immediate and sustained release liquisolid formulations revealed a characteristic broad peak at 167^{0} C, and the area and sharpness of the

peak decreased when compared to that of the drug alone. This indicates change in the crystalline nature of the drug. No other peaks were observed in the liquisolid formulation indicating there is no interaction between drug and excipients.

3.7 Stability Studies:

Subjecting the liquisolid compacts to stability studies as per ICH guidelines reported that storage at accelerated conditions has no effect on the hardness, drug release profiles and drug content of liquisolid compacts indicating physical stability. However further studies are required to establish the same.

The results of Stability studies of optimized formulation of immediate release compact (S-8) and mucoadhesive sustained release compact MHP-4 were reported in Table 13 & 14 respectively.

Table-13: Stability studies of optimized formulation of immediate release compact (S-8).

Time (months)	% Drug release	Hardness (kg/cm^2)	Content uniformity (%)
0	100.15 ±0.10	4.5±0.15	100.22 ±0.10
1	100.10±0.15	4.5±0.10	100.15±0.15
2	100.00±0.15	4.48±0.10	100.00±0.20
3	99.89 ±0.10	4.48±0.15	99.98 ±0.10

Table-14: Stability studies of optimized formulation of sustained release compact (MHP-4).

Time (months)	% Drug release	Hardness (kg/cm^2)	Content uniformity (%)
0	100.00 ±0.10	4.90±0.15	100.20 ±0.10
1	99.90±0.15	4.90±0.15	100.15±0.20
2	99.55±0.10	4.90±0.10	100.03±0.10
3	98.90 ±0.10	4.80±0.10	99.95 ±0.20

Conclusion:

Immediate release and mucoadhesive sustained release formulations of Itraconazole were successfully formulated using liquisolid technology. PEG 600 & propylene glycol was selected as nonvolatile solvent for immediate and sustained release compacts respectively. From the post compression evaluation data it was observed that the percentage drug release

for immediate release compact S-8 (optimized) was found to be 100% within 45 mins and whereas marketed capsule (SPORONOX) reported 100% drug release after 90 mins. The mucoadhesive sustain release compact MHP-4(HPMC K4M as polymer/carrier) was selected as the optimized formulation which has the linearity following zero order kinetics with R^2 value of 0.997, having sustained activity upto 8 h with greater mucoadhesion property. The results of XRD reported change in the crystalline properties of drug resulting in amorphous state and DSC profile reported that there is no interaction between drug and excipients during formulation process. In conclusion it can be stated that the objective of the study was met. The technique was successful in improving the dissolution rate as well as sustaining the drug release by improving the bioavailability of Itraconazole which when formulated into a mucoadhesive sustain release compact to increase the gastric residence time.

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