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Impact of 1% SLS on Fast Release Deferiprone and Sustained Release Domperidone Dual-Layer Tablet

Dr. Shahid Mohd, Zaineb Sheheryar

Deccan School Of Pharmacy, Dar-Us-Salam. Aghapura, Hyderabad, 500001, India

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ABSTRACT

The aim of the study was to design and evaluate bilayer tablets of Deferiprone as immediate release and quick relief and Domperidone for sustained release and check the effect of 1% SLS for immediate release action. Bilayer tablets was prepared using direct compression method. Super disintegrants such as Crospovidone, Croscarmellose sodium and Sodium starch glycolate were evaluated for immediate release of deferiprone. Polymers HPMC K4, HPMC K15 and HPMC K100 for controlling release of Domperiodone. The compressed bilayer tablets were evaluated for weight variation, thickness, hardness, friability, drug content and in vitro drug release in 0.1N HCl and phosphate buffer pH 6.8. All the pre and post compression parameters were found to be within the acceptable limits. The formulations were optimized based on results of dissolution and formulations F6 for immediate release & F6D3 for sustained release. F7D3 was formulated with addition of 1% SLS and showed better dissolution and compared to F6D3. The release kinetics of Domperiodne was subject to curve fitting analysis in order to identify the best fit kinetic model. The regression analysis proves that F6D3 follow first order release and drug release by diffusion process based on Fick's law of diffusion. The data for stability studies infer no considerable change in drug content, dissolution rates and other quality control test were within limits.

Keywords: Bilayer Tablets, Deferiprone, Domperidone, Direct Compression Method

INTRODUCTION

Bilayer tablets are a type of oral solid dosage form consisting of two layers of compressed powders or granules of different drug substances that are arranged in a sandwich-like structure. The bilayer tablet is designed in a way that each layer can be made of different drug formulations, allowing for a combination of drugs with different release profiles or therapeutic effects.

The upper layer of the bilayer tablet is usually designed for immediate release of the drug substance, while the lower layer is formulated for delayed release or sustained release of the drug substance. The immediate-release layer provides a quick onset of action, while the delayed-release layer provides a prolonged duration of action.

Bilayer tablets are commonly used in the pharmaceutical industry for various therapeutic applications and offer several advantages over conventional single-layer tablets, such as improved drug efficacy, reduced side effects, and better patient compliance.

Thalassemia is an inherited disorder that is life long and patient has to go under blood transfusions which lead to iron overload. Deferiprone drug of BCS class III with dose 500mg, 1.8 hrs half and 30% bioavailability have ideal characteristics for immediate release layer. Therefore, it might be more suitable to incorporate clopidogrel as an immediate release layer in the bilayer tablet formulation. This would allow for rapid drug release and absorption into the bloodstream to achieve its desired effect promptly.

One of the major drawbacks of the drug Deferiprone is that it causes GIT irritation Hence Domperidone in combination is given with Deferiprone that can reduce this drug induced side effect. Domperidone is a BCS class II drug with dose 10 mg, 7 hours half-life and 15% bioavailability have ideal characteristics for sustained release. This would result in a slower and controlled drug release over an extended period, helping to maintain a consistent and provide prolonged antinausea effects.

Therefore, an attempt has been made in the combination of bilayer tablets of Deferiprone and Domperidone.

METHODOLOGY

PRE-FORMULATION STUDIES-DEFERIPRONE AND DOMPERIDONE

Preformulation may be described as a phase of their search & development process where the formulation scientist characterizes the physical, and chemical properties of API, to develop stable, safe and effective dosage forms. During this evaluation possible interaction with various inert ingredients intended for use in the final dosage.

1. Organoleptic Properties:

The colour, odour and Appearance of the drug are evaluated using descriptive terminology.

2. Melting Point:

✓ The melting point of the drug is found by using the Melting/Boiling Point Apparatus.

✓ The drug can be transferred to the melting point apparatus using a capillary tube and the temperature can be gradually increased until the mixture melts.

✓ The melting point can be determined by observing the changes in the physical state of the drug and recording the temperature range at which the melting occurs.

3. Solubility Analysis:

The solubility of the drug was determined by an equilibrium method using the following solvents.

- **Distilled Water,**
- **Methanol,**
- **Phosphate Buffer 6.8 And**
- **0.1N HCL Buffer**

– Prepare a series of solutions containing 5ml of solvents in test tubes.

– Place 5mg of the API in each solution and dissolve using the handshake method until it is completely dissolved.

– Then keep on increasing until saturation is achieved.

4. Construction Of Standard Curve For Deferiprone And Domperidone:

Determination Of λ Max

Preparation Of Standard Stock Solution, Working Standard And Dilutions:

- 50 mg of Drug was dissolved in 50 ml of 0.1 N HCl to give a concentration of 1000 µg/ml.
- From the above solution 1 ml was withdrawn and made to 10 ml with 0.1 N HCl to give a concentration of 100 µg/ml.
- From the above solution concentration of 5,20,15,20,25 were prepared.

Scanning:

The UV scan was taken between 200 to 400 nm.

5. FTIR Studies:

FTIR studies are performed on drug alone and drug-excipient mixture. About 0.1-1.0% sample was well mixed with KBr powder which was put into a pellet-forming die and by applying a force of 8 tons under vacuum, transparent pellets were obtained. Analysis was done on 4000-400 cm -1 wave number range samples.

6. PRE-COMPRESSION EVALUATION FOR BOTH DRUGS

(i) Loss On Drying:

It was determined on 1 g by drying in an oven at 100°C to 105°C for 3 hours. Mixed and accurately weighed the substance to be tested. Tare a glass stopper, a shallow weighing bottle that has been dried for 30 minutes under the same conditions to be employed in the determination and weigh the empty bottle (W1). Put the sample in the bottle, replace the cover, and accurately weigh the empty bottle's contents (W2).

By gentle, sidewise shaking, the sample was as evenly as practicable to a depth of about 5 mm. Placed the loaded bottle in the drying chamber. Dried the sample at the specified temperature in a desiccator before weighing. Weighed the bottle (W3). The difference between successive weights should not be less than 0.3%. The loss on drying is calculated by the formula:

$$\% \text{ LOD} = \frac{(W2 - W3)}{(W2 - W1)} \times 100$$

Where, W1 = Weight of empty weighing bottle

W2 = Weight of weighing bottle + sample

W3 = Weight of weighing bottle + dried sample

(ii) Drug Powder Characterization: Angle Of Repose:

The angle of repose is the maximum angle of a stable slope determined by friction, cohesion and the shapes of the particles. The internal angle between the surface of the pile and the horizontal surface is known as the angle of repose and is related to the density, surface area and coefficient of friction of the raw material.

$$\Theta = \tan^{-1}(h/r)$$

Where, h = height of heap,

r = radius of heap,

Θ = angle of repose.

Table 1: Limits

Angle of flow property
<25° Excellent
25-30° Good
30-40°Passable
>40° Very poor

(iii) Bulk Density:

Bulk density is defined as the mass of the powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particle becomes more spherical, bulk density is increased. In addition, as the granule size increases bulk density decreases.

A quantity of 5 gm of powder was weighed and transferred to a measuring cylinder and observed the volume occupied by the sample. The initial volume was calculated. Bulk density was calculated using the formula.

Bulk density = Bulk mass / Bulk volume

(iv) Tapped Density:

Tapped density is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped and volume readings are taken until little further volume changes are observed the mechanical tapping is achieved by raising the cylinder and allowing it to drop under its weight a specific distance device that rotates the device during tapping may be preferred to minimize any possible separation of the mass during tapping down.

The powder in the measuring cylinder was tapped for specific times at a height of 2.5 cm at an interval of 2 seconds. The powder in the graduated cylinder was tapped for specific times at a height of 2.5 cm at an interval of 2 seconds. The final volume occupied by the sample was noted and tapped density was calculated by using the formula:

Tapped density = m/ vf

Where, m = initial weight of material in gm,

Vf = volume of material after tapping.

Generally, replicate determinations are desirable for the determination of this Property.

(v) Measurement Of Powder Compressibility:

Carr's Index

Based on the apparent bulk and the tapped density, the percentage compressibility of bulk was determined by the following formula.

Carr's index: =100 (V0-Vf) /V0

Where, Vf = final tapped volume,

Vo = initial un-tapped volume

Table 2: Limits

SNO	Compressibility index	Flow
1	5-`12	Free flow
2	13-16	Good flow
3	17-22	Fair
4	22-25	Poor
5	26-39	Very poor
6	>40	Extremely poor

(vi) Hausner Ratio

Based on the apparent bulk and the tapped density, the percentage compressibility of bulk was determined by the following formula.

Hausner Ratio: =V0/ Vf

Where, Vf = final tapped volume,

Vo = initial un-tapped volume.

Table 3: Limits:

SNO	Hausner's ratio	Flow
1	1-1.2	Free-flowing
2	1.2-1.61	Cohesive powder

7. FORMULATION OF BILAYER TABLET

(i)Preparation Of Bilayer Tablet:

To produce bilayer tablets, layers of sustained release and immediate release were mixed. Granules for the bottom layer are dosed into the die from the first hopper. The powder blend for the immediate release layer was poured into the die containing the originally compressed matrix tablet using a multi-station punching machine equipped with flat punches after the first layer's pre-compression.

(ii) Modified formulation: Addition of 1%SLS:

One percent of SLS was added to the optimised formulation to track and monitor its dissolution.

Table 4 Formulation of immediate release tablet -Total 650 mg

Ingredients	F1	F2	F3	F4	F5	F6	F7
IR Release							
Deferiprone	500	500	500	500	500	500	500
Sodium Bicarbonate	26	32.5	26	32.5	26	32.5	26
MCC	92.5	76	92.5	76	92.5	76	74.5
SSG	25	35	-	-	-	-	-
CCS	-	-	25	35	-	-	-
CP	-	-	-	-	25	35	35
Magnesium Stearate	6.5	6.5	6.5	6.5	6.5	6.5	6.5
SLS	-	-	-	-	-	-	1.5
Total Weight	650	650	650	650	650	650	650

Ingredients	D1	D2	D3	D4	D5	D6
IR Release						
Deferiprone	500	500	500	500	500	500
Sodium Bicarbonate	32.5	32.5	32.5	32.5	32.5	32.5
MCC	76	76	76	76	76	76
CP	35	35	35	35	35	35
Magnesium Stearate	6.5	6.5	6.5	6.5	6.5	6.5
Total Weight	650	650	650	650	650	650
SR Release						
Domperidone	10	10	10	10	10	10
MCC	131	128.5	131	128.5	131	128.5
HPMC-K4	7.5	10	-	-	-	-
HPMC-K15	-	-	7.5	10	-	-
HPMC-K100	-	-	-	-	7.5	10
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5
Total Weight	`150	150	150	150	150	150

8. POST-COMPRESSION STUDIES-EVALUATION OF BILAYER

All the prepared bilayer tablets were evaluated for the following parameters.

(i) Appearance:

The bilayer tablets were identified visually by checking the colour difference.

(ii) Thickness:

Thickness was measured using a vernier calliper. Five tablets of the formulation were picked randomly and thickness was measured individually.

(iii) Hardness:

Hardness was measured using a Monsanto hardness tester. For each batch, three tablets were tested.

(iv) Friability:

Twenty tablets were weighed and placed in the Roche friability and the apparatus was rotated at 25 rpm for 4 minutes. After revolutions, the tablets were weighed again. The percentage friability was measured using the formula,

$$\% F = \{1-(Wt/W)\} \times 100$$

Where, % F = Friability in percentage

W = Initial weight of tablets

Wt = Weight of tablets after the revolution

(v) Weight Variation:

Ten tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets were calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight.

(vi) Disintegration Test:

For a drug to be absorbed from a solid dosage form after oral administration, it must be in solution, and the first important step toward this condition is usually the break-up of the tablet; a process known as disintegration. The disintegration test is a measure of the time required under a given set of conditions for a group of tablets to disintegrate into particles which will pass through a 10 mesh screen. Generally, the test is useful as a quality assurance tool for conventional dosage forms.

(vii) *In-Vitro* Dissolution Studies For IR:

Dissolution of the tablets was carried out on USP dissolution type II apparatus using a paddle. 900 ml of pH 1.2 buffer (0.1N HCL) as dissolution medium was filled in a dissolution vessel and the temperature of the medium was set at 37 ± 0.5°C. The rotational speed of the paddle was set at 100 rpm. 5 ml of sample was withdrawn at a predetermined time interval of up to 90 minutes and the same volume of fresh medium was replaced. The withdrawn samples were diluted to 10 ml with 0.01N HCL, filtered and analyzed on a UV spectrophotometer at 242 nm using 0.1 N HCL as a blank. Percentage cumulative drug release was calculated.

(viii) *In-Vitro* Dissolution Studies For SR:

Dissolution of the tablets was carried out on USP dissolution type II apparatus using a paddle900 ml of pH 1.2 buffer (0.1 N HCL) as dissolution medium was filled in a dissolution vessel and the temperature of the medium was set at 37 ± 0.5°C. The rotational speed of the paddle was set at 100 rpm. 5 ml of sample was withdrawn at predetermined time intervals up to 12 hr and the same volume of fresh medium was replaced. The withdrawn samples were analyzed on a UV spectrophotometer at 242 nm using 0.1 N HCL as a blank. The percentage of cumulative drug release was calculated.

(ix) *In-Vitro* Dissolution Study Of Bilayer Tablet:

The dissolution studies of optimised deferiprone and domperidone bilayer tablets were studied by conducting dissolution using USP dissolution type II apparatus using a paddle. The medium was filled up to 900 ml of pH 1.2 buffer (0.1N HCL) as a dissolution medium Deferiprone is more soluble in acidic environments and less in neutral or slightly basic conditions like a phosphate buffer at pH 6.8. as it is soluble in 0.1 N HCL and domperidone is highly soluble in 0.1 N HCL. The temperature of the medium was set at 37 ± 0.5°C. The rotational speed of the paddle was set at 100 rpm. 5 ml of sample was withdrawn at predetermined time intervals up to 12 hr and the same volume of fresh medium was replaced. The withdrawn samples were analyzed on a UV spectrophotometer at 200-400 nm using 0.01N HCL as a blank. The percentage of cumulative drug release was calculated.

DETAILS OF DISSOLUTION TEST:

Dissolution test apparatus	: USP XX III
Speed	: 100 rpm
Stirrer	: Paddle type
Volume of medium	: 900 ml
Volume withdrawn	: 5 ml
Medium used	: 0.1N HCL, Phosphate buffer 6.8
Buffer temperature	: 37 ± 0.5° C

9. DATA ANALYSIS:

The following plots were made: cumulative % drug release vs time (zero-order kinetic model); log cumulative of % drug remaining vs time (first-order kinetic model); cumulative % drug release vs square root of time (Higuchi model); cumulative % drug release vs time (Peppas model). The regression coefficient R2 value nearer to 1 indicates the model best fits the release mechanism.

(i) Zero-order kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation,

$$Q_t = Q_0 + K_0 t$$

Where Q_t = amount of drug dissolved in time t.

Q_0 = initial amount of the drug in the solution and

K_0 = zero order release constant.

(ii) First-Order Kinetics:

To study the first-order release rate kinetics, the release rate data were fitted to the following equation,

$$\text{Log } Qt = \log Qo + K1t/2.303$$

Where Qt is the amount of drug released in time t,

Qo is the initial amount of drug in the solution and

K1 is the first-order release constant.

(iii) Higuchi Model:

Higuchi developed several theoretical models to study the release of water-soluble and low-soluble drugs incorporated in semisolids and/or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. The equation is,

$$Q_T = K_H \cdot t_{1/2}$$

Where Q_T = amount of drug released in time t,

K_H = Higuchi dissolution constant.

(iv) Krosmeyer And Peppas Release Model:

To study this model the release rate data are fitted to the following equation,

$$Mt / M\infty = K \cdot t^n$$

Where $Mt / M\infty$ is the fraction of drug release,

K is the release constant, t is the release time and n is the diffusional coefficient for the drug release that is dependent on the shape of the matrix dosage form.

10. STABILITY STUDIES OF THE OPTIMIZED FORMULATION:

The stability of a pharmaceutical preparation can be defined as “the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life.” The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf-lives to be established. ICH specifications for stability study.

Procedure:

In the present study, the formulations F6 and D3 were selected and the stability studies were carried out at 25±20C, 60±50C % RH (Long-term stability condition), 30 ±20C, 65±50C % RH (intermediate condition) and 40±20C, 75±50C (accelerated conditions), the tablets were packed in amber colour screwcap container and kept in above said condition for a period of six months. The tablets were analyzed periodically for their physical appearance and in-vitro drug release.

Evaluation of samples:

The samples were analyzed for the following parameters:

I. Physical evaluation:

Appearance: The samples were checked for any change in colour at an interval of 1 month up to 3 months.

Hardness: The samples were tested for hardness at an interval of 1 month up to 3 months.

II. Chemical evaluation:

Drug content: The samples were checked for drug content at an interval of 1 month up to 3 months.

Drug release: The samples were subjected to drug release studies at an interval of 1 month up to 3 months.

RESULTS AND DISCUSSION:

1. Organoleptic Properties Table 5

S No.	Properties	Deferiprone	Domperidone
1	State	Solid	Solid
2	Colour	White To Pinkish white	White
3	Odor	Odorless	Odorless
4	Appearance	Fine crystalline powder	Fine crystalline powder

2. Solubility Analysis Table 6

Medium	Solubility of Deferiprone	Solubility of Domperidone
Distilled Water	14.3 mg/ml±0.78	0.00095 mg/ml ±0.31
Methanol	13.9 mg/ml±0.11	1.17 mg/ml ±0.62
Phosphate Buffer 6.8	16 mg/ml ±0.65	32.52 mg/ml ±0.14
0.1 N HCl	32.7 mg/ml ±0.88	0.423 mg/ml ±0.24

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3. Melting Point: Table 7

Drug	Reference Range	Observed Range
Deferiprone	272°C – 278°C	275°C
Domperidone	242.5 °C	242°C

4. Determination Of λ Max (Wavelength)

Deferiprone: Table 8

Drug	Reference Range	Observed Range
DEFERIPRONE	279	278

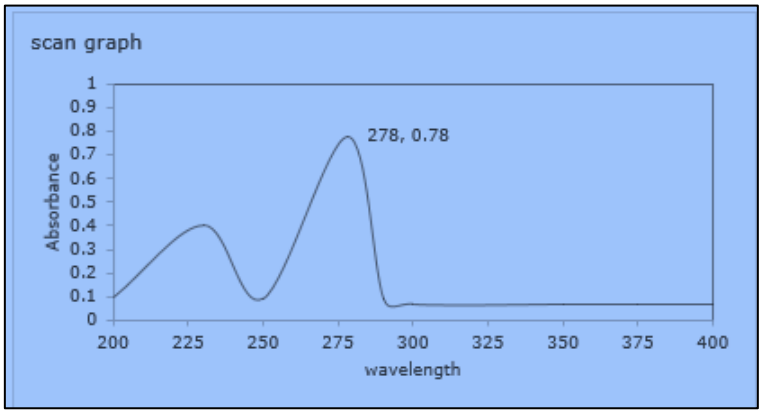

Fig 1

Calibration Curve: Table 9

Concentration (mg/ml)	Absorbance
5	0.175±0.011
10	0.292±0.012
15	0.45±0.016
20	0.601±0.010
25	0.75±0.08

All values are expressed as mean ± SD(n=3)

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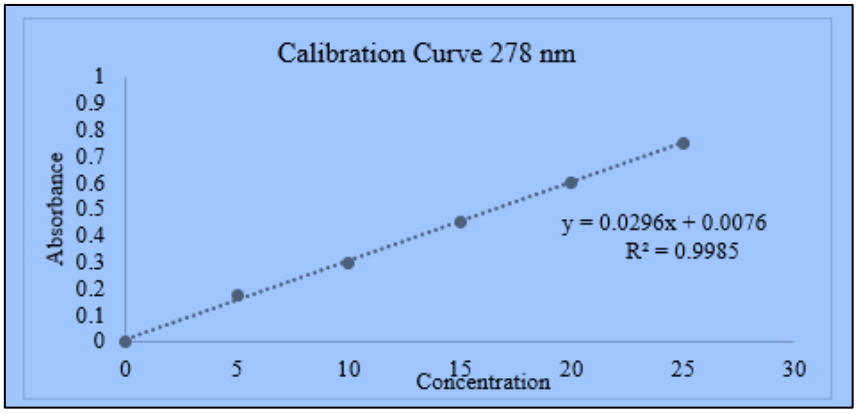

Fig 2 The Standard Deferiprone Graph Demonstrated Strong Linearity with an R^2=0.9922, Signifying Its Adherence To The "BEER-LAMBERT's Law"

Domperidone: Table 10

Drug	Reference Range	Observed Range
Domperidone	230-252	230

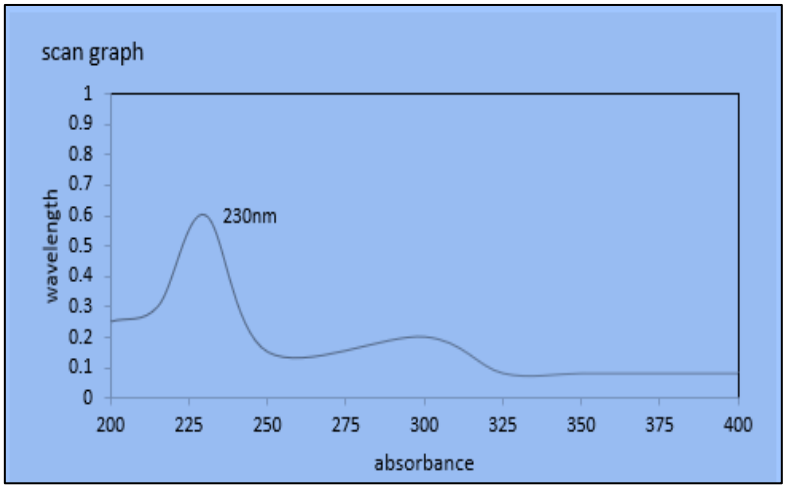

Fig 3

Calibration Curve Table 11

Concentration(mg/ml)	Absorbance
5	0.224±0.032
10	0.354±0.017
15	0.54±0.011
20	0.701±0.016
25	0.856±0.064

All values are expressed as mean ± SD(n=3)

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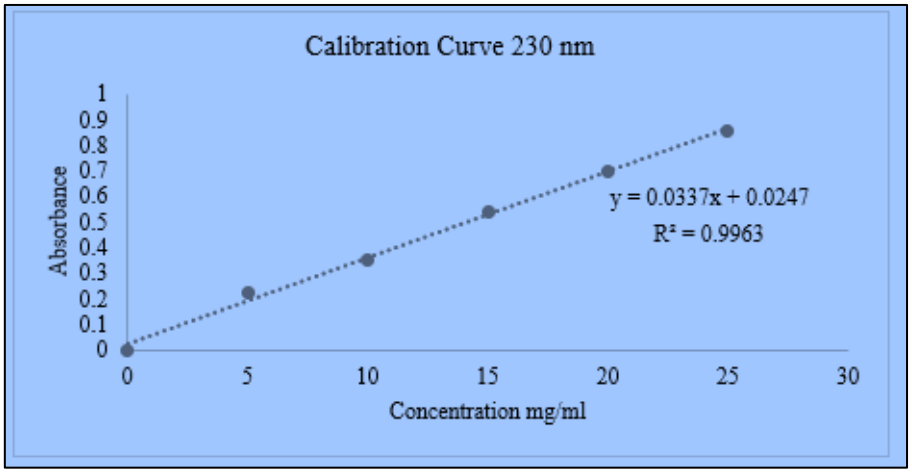

Fig 4 The Standard Deferiprone Graph Demonstrated Strong Linearity with an R^2= 0.9963, Signifying Its Adherence To The "BEER-LAMBERT'S LAW

5. FTIR STUDIES

Deferiprone

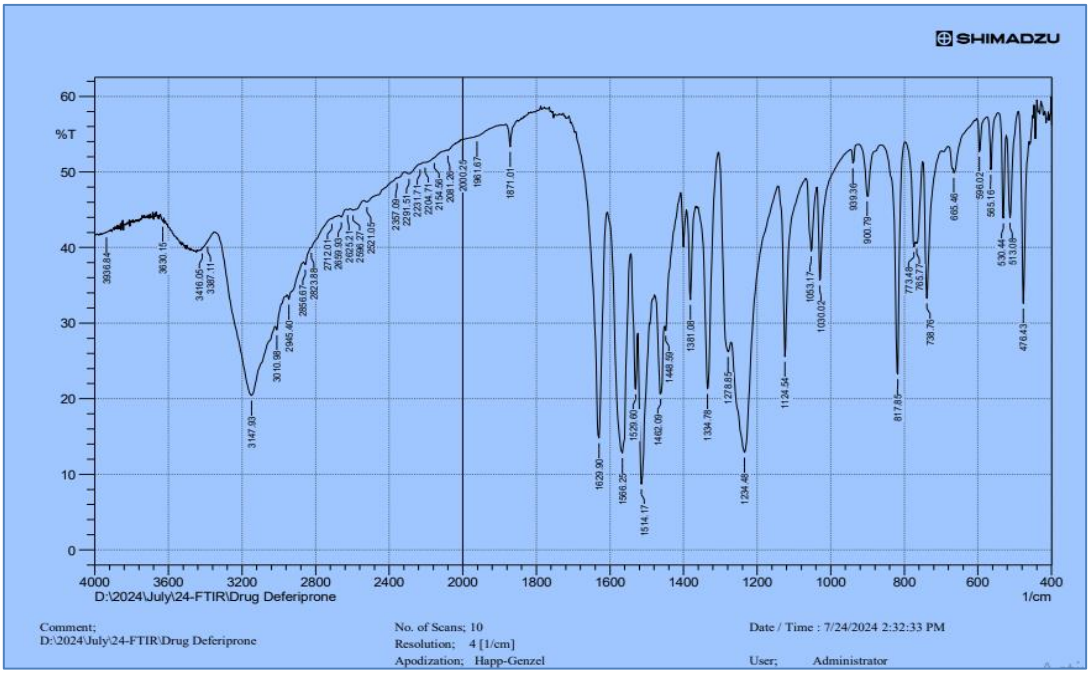

Fig 5 FTIR of Drug Deferiprone

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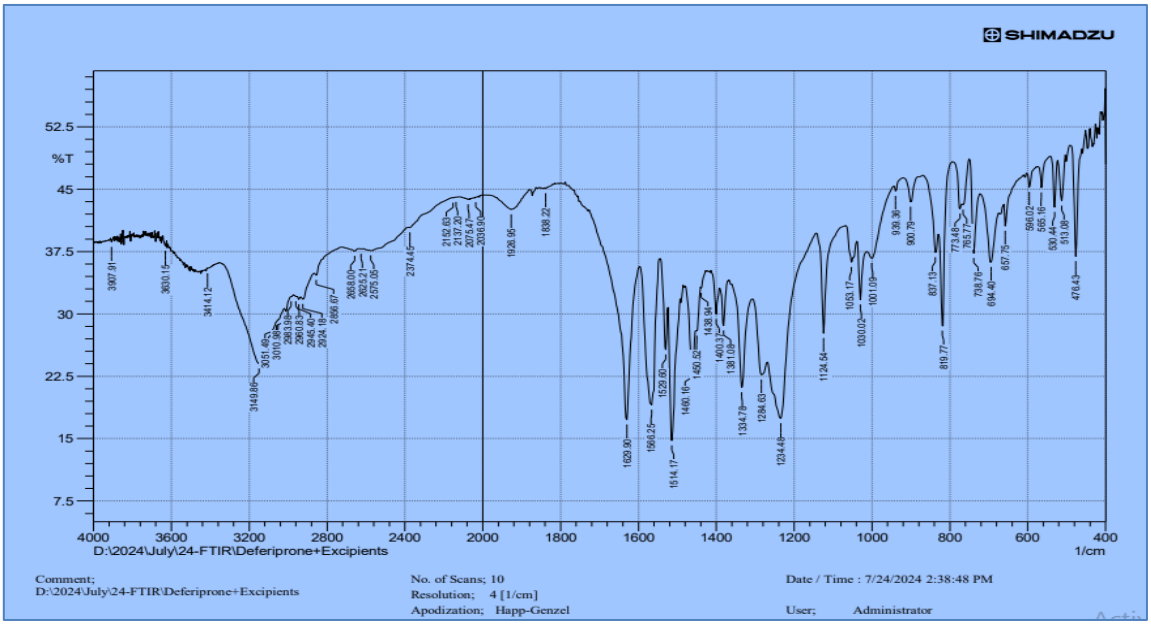

Fig 6 FTIR of Drug Deferiprone+ Excipients

Table 12

Sno	Group	Standard Drug Peaks cm^{-1}	Drug + Excipients Peaks cm^{-1}
1	O-H(ALCOHOL)	3416.05	3414.12
2	C-H(ALKANE)	738.76	738.76
3	C=C(AROMATIC)	1566.25	1566.25
4	C=H(AROMATIC)	3010.98	3010.98
5	C-O(ETHER)	1030.2	1030.2
6	C-Cl(ALKYL HALIDE)	2945.40	2945.40

Domperidone

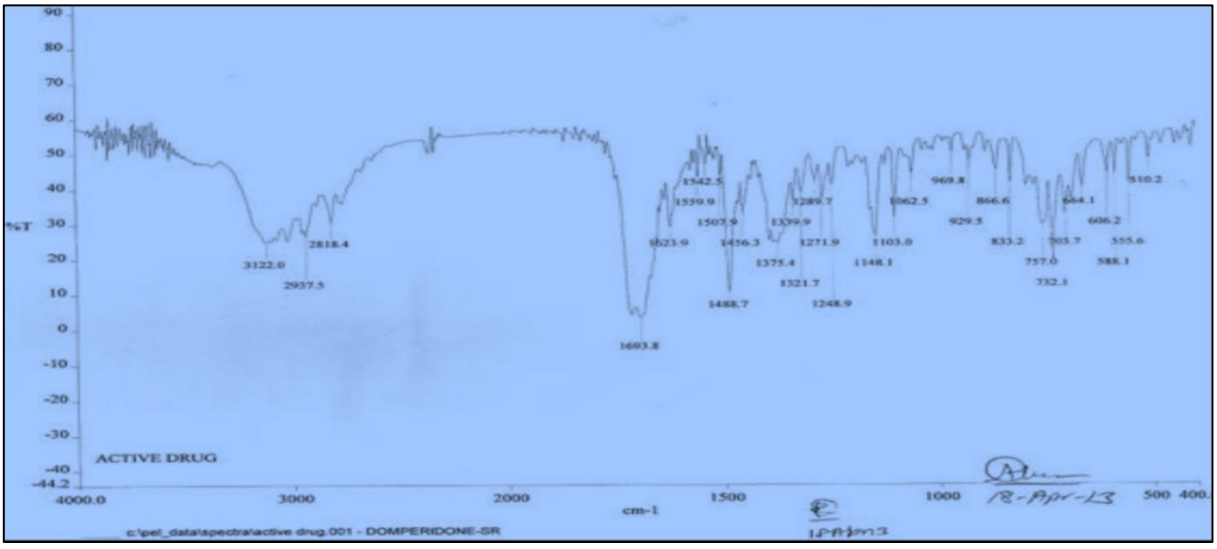

Fig 7 FTIR of DRUG Domperidone

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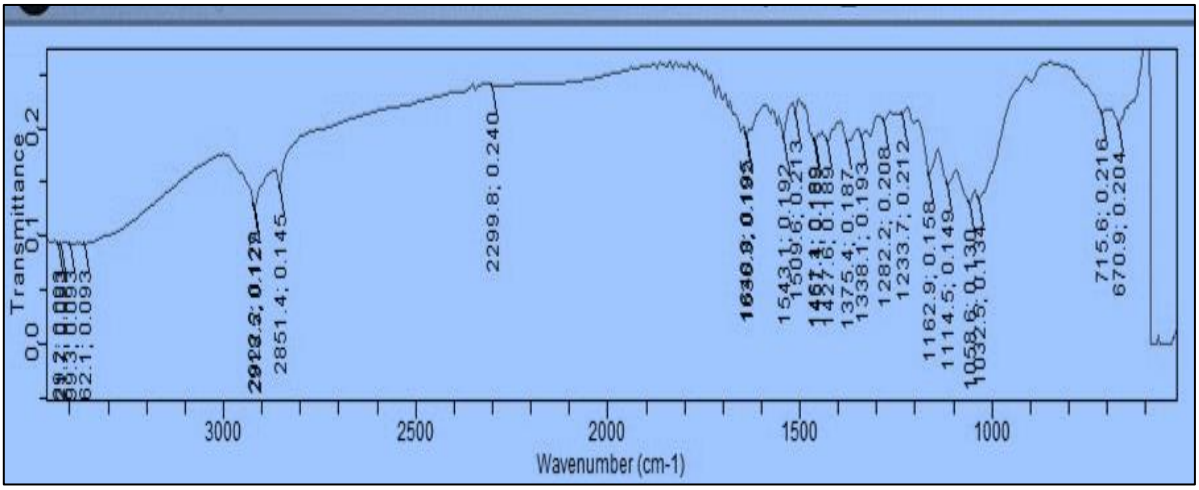

Fig 8 FTIR of Drug Domperidone + Excipients

Table 13

Sno	Group	Standard Drug Peaks cm^{-1}	Drug + Excipients Peaks cm^{-1}
1	O-H(ALCOHOL)	1062	1058
2	C-H(ALKANE)	2937.5	2928.0128
3	C-N(AMIDE)	1339.9	1338.1
4	C=C(AROMATIC)	1542.5	1543.1
5	C-O(ETHER)	1289.7	1282.2
6	C-Cl(ALKYL HALIDE)	664.1	670.9

6 & 8. Evaluation of pre- and post-compression parameters for both drugs

Loss on Drying: Table 14

Loss on Drying	Deferiprone	Domperidone
Not more than 0.5%	0.45%	0.43%

Drug Powder Characterization: Table 15

Material	Angle of repose
Deferiprone	27°32'
Domperidone	27°54'

The results indicated that the raw material had good flow properties

Flow Properties: Table 16

Material	Bulk Density	Tapped Density	Carr's index	Hausner Ratio
Deferiprone	0.318	0.412	11.11	1.14
Domperidone	0.373	0.422	10.82	1.13

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Pre-compression Evaluation Of Deferiprone

Table 17: Results of precompression evaluation of Deferiprone immediate release layer.

Code	Angle of Repose ±SD	Bulk Density (g/ml) ±SD	Tapped Density (g/ml) ±SD	Carr's Index. (%) ±SD	Hausner's ratio ±SD
F1	27°33'±0.26	0.318±0.032	0.412±0.031	11.11±0.12	1.14±0.011
F2	25°35'±0.25	0.353±0.028	0.431±0.018	13.31±0.16	1.13±0.027
F3	28°13'±0.11	0.371±0.011	0.412±0.033	10.45±0.35	1.15±0.018
F4	27°54'±0.36	0.372±0.017	0.422±0.022	10.47±0.16	1.12±0.024
F5	25°63'±0.24	0.383±0.023	0.433±0.017	11.78±0.11	1.12±0.036
F6	26°41'±0.27	0.376±0.018	0.435±0.028	13.02±0.16	1.14±0.019
F7	25°41'±0.56	0.287±0.027	0.524±0.037	12.05±0.14	1.13±0.021

Post Compression Evaluation Of Deferiprone

Table 18: Results of post-compression evaluation of Deferiprone immediate release layer.

Formulation code	Average weight (mg)	Thickness (mm)	Hardness Kg/cm2	Friability (%)	Disintegration Time	Drug content (%)
F1	650.2	2.9	7.3	055	21 sec	99.4
F2	649.5	3.3	7.2	0.58	25 sec	97.43
F3	649.2	3.1	7.2	0.57	24 sec	99.63
F4	648.4	2.8	7.4	0.54	22 sec	98.27
F5	649.8	3.2	7.3	0.57	23 sec	99.51
F6	650.4	2.9	7.4	0.51	20 sec	99.72
F7	650.2	2.8	7.3	0.53	21 sec	99.89

Pre-compression Evaluation Of Domperidone

Table 19: Results of precompression evaluation of domperidone sustained release layer

Formulation Code	Angle of Repose ±SD	Bulk Density (g/ml) ±SD	Tapped Density (g/ml) ±SD	Carr's Index. (%) ±SD	Hausner's ratio ±SD
D1	27°53'±0.36	0.373±0.017	0.423±0.022	10.82±0.18	1.11±0.024
D2	25°57'±0.24	0.386±0.023	0.436±0.017	11.12±0.11	1.13±0.036
D3	24°31'±0.23	0.364±0.032	0.423±0.024	13.14±0.25	1.14±0.031
D4	26°41'±0.28	0.377±0.018	0.436±0.028	13.52±0.16	1.14±0.017
D5	25°42'±0.25	0.376±0.024	0.427±0.023	13.13±0.18	1.12±0.023
D6	26°42'±0.26	0.377±0.028	0.434±0.027	12.16±0.118	1.14±0.022

Post Compression Evaluation Of Domperidone

Table 20: Results of post-compression evaluation of domperidone sustained release layer

Formulation code	Average weight (mg)	Thickness (mm)	Hardness Kg/cm2	Friability (%)	Drug content (%)
D1	149.9	2.86	5.98	0.59	99.93
D2	148	3.12	5.83	0.58	99.81
D3	150	2.89	6.1	0.59	99.83
D4	149.9	2.80	5.78	0.59	99.94
D5	150	2.95	6.78	0.58	98.93
D6	149.8	3.11	5.32	0.58	97.7

Post Compression Evaluation Of Bilayer Formulation

Table 21: Results of post-compression evaluation of Bilayer formulation

Formulation code i)F6 D3	Average weight(mg)	Mean Hardness (Kg/cm^2)	Thickness (mm)	Friability % w/w	Drug content (%)
1	**800.1**	**6.4**	**2.92**	**0.55**	**100.3**
2	799.6	6.2	2.94	0.56	100.2
3	800	6.4	2.93	0.56	100.1
4	798.9	6.3	2.98	0.54	100.0
5	790.2	6.4	2.92	0.53	100.3
ii)F7D3					
1	800.2	6.2	2.93	0.54	99.89
2	800.5	6.3	2.96	0.53	98.99
3	749.2	6.4	2.91	0.51	100.1
4	748.6	6.1	2.94	0.57	99.32
5	**800.1**	**6.3**	**2.92**	**0.58**	**100.2**

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***IN-VITRO* DISSOLUTION STUDIES**

***In-Vitro* Drug Release Data Of Deferiprone Immediate Layer: Table 22**

Time (in mins)	F1	F2	F3	F4	F5	F6
5	24.44±0.522	26.43±0.433	16.35±0.426	15.25±0.424	30.59±0.637	**33.77±0.524**
10	36.44±0.522	26.42±0.545	33.75±0.524	37.77±0.621	49.73±0.874	**56.38±0.324**
15	59.65±0.412	61.64±0.875	47.44±0.438	52.35±0.419	79.28±0.374	**77.22±0.318**
20	75.00±0.321	72.22±0.346	56.38±0.324	62.21±0.248	83.22±0.892	**90.21±0.421**
30	83.94±0.348	80.93±0.762	65.87±0.523	77.22±0.318	93.32±0.839	**99.72±0.621**
40	91.13±0.129	90.12±0.487	67.63±0.491	79.24±0.312	99.51±0.983	**99.72±0.621**
50	96.48±0.246	97.43±0.983	76.65±0.483	83.56±0.429	99.51±0.983	**99.72±0.621**
60	99.44±0.522	97.43±0.983	80.86±0.394	94.64±0.326	99.51±0.983	**99.72±0.621**
75	99.44±0.522	97.43±0.983	92.07±0.429	98.27±0.421	99.51±0.983	**99.72±0.621**
90	99.44±0.522	97.43±0.983	99.63±0.248	98.27±0.421	99.51±0.983	**99.72±0.621**

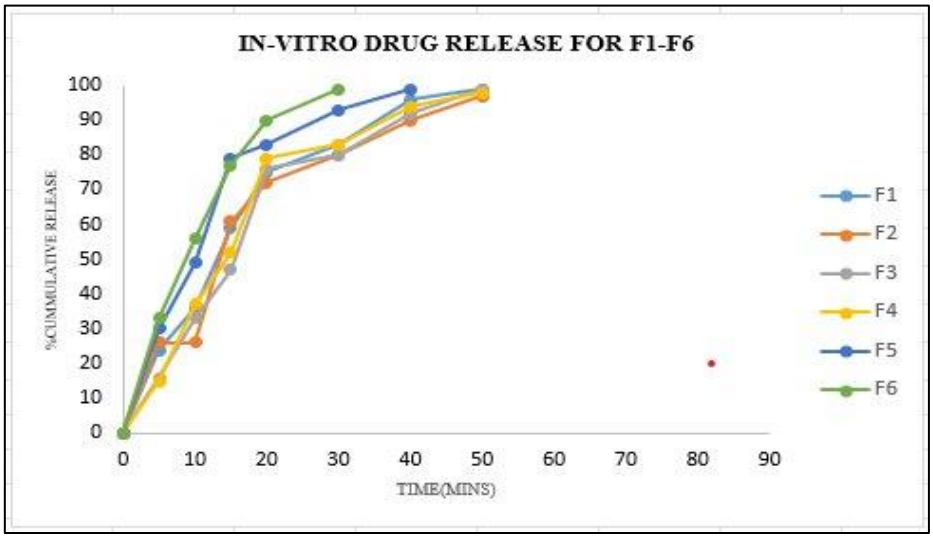

Fig 9 Cumulative per cent drug release versus time plots of Deferiprone tablets: F1-F6 where in F6 shows best result for immediate release

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Cumulative per cent drug release of Domperidone sustained layer: Table 23

Time (in hrs)	D1	D2	D3	D4	D5	D6
0.5	5	6	**4**	5	3	4
1	32.13	22.24	**14.64**	24.67	14.03	22.13
2	50.87	47.57	**20.47**	38.46	21.35	39.94
4	69.86	72.53	**30.99**	51.99	35.77	57.66
6	88.35	88.41	**49.13**	72.17	52.02	69.58
8	99.93	99.81	**64.26**	86.62	88.13	85.84
10	99.93	99.81	**87.41**	99.94	98.93	97.7
12	99.93	99.81	**99.83**	99.94	98.93	97.7

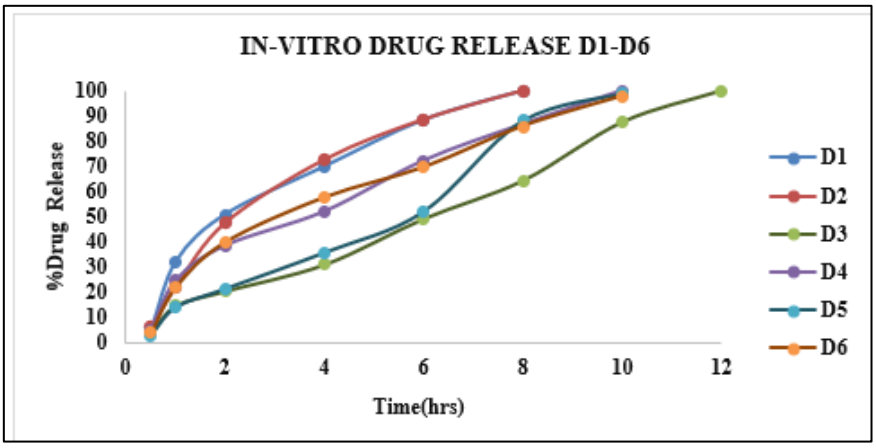

Fig 10 Cumulative per cent drug release versus time plots of Domperidone tablets: D1-D6 where in D3 shows best result for sustained release

***In-Vitro* Drug Release Profile Of Optimised Formulation(F6D3)**

Among the formulations are the D3 formulation for continuous release and the F6 formulation for quick release, both of which comprise HPMC-K15 as a binder and Crospovidone as a super-disintegrant. MCC, sodium bicarbonate, and magnesium stearate were chosen as optimal formulations.

Table 24:

Time (Hrs)	%Percentage Drug Release	
	Deferiprone(F6)	Domperidone(D3)
0	0	0
0.5	99.87	4
1	-	14.64
2	-	20.47
4	-	30.99
6	-	49.13
8	-	64.26
10	-	87.41
12	-	99.83

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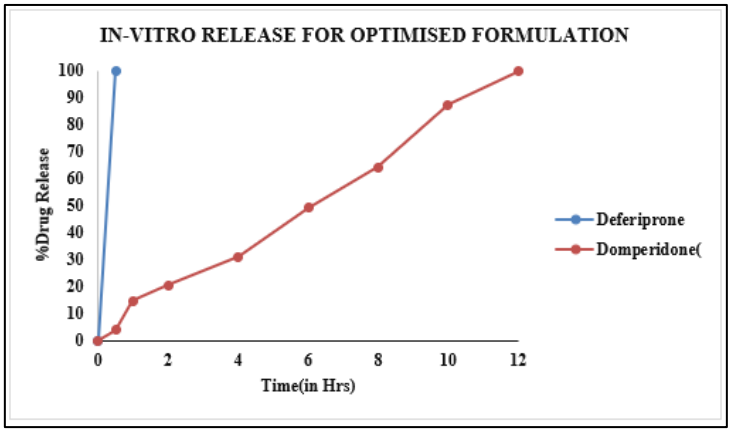

Fig 11 In-vitro dissolution profile of optimized bilayer tablets

***In-Vitro* Drug Release Profile For F6D3 And F7D3 For Comparison**

Table 25:

Time(in mins)	F6D3	F7D3
5	33	45
10	58	67
15	79	86
20	93	98
30	99	99
40	100	100
50	100	100
60	100	100
75	100	100
90	100	100

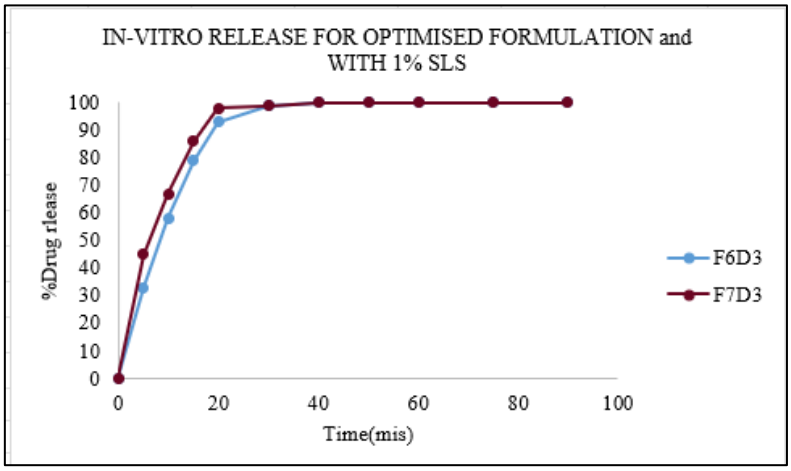

Fig 12: In-Vitro Release For Optimised Formulation And With 1% SLS

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9. Drug Release Kinetics Of Sustained Release Layer Of Bilayer Tablet

Table 26: Release kinetics of optimised Bilayer Tablets

PARAMETERS	Zero-order	First order	Higuchi	Peppas
	% CDR Vs T	Log % C Vs T	%CDR Vs √T	Log C Vs Log T
Slope	8.1974	0.1434	29.349	1.1602
Intercept	1.5714	0.4526	14.328	0.7721
R^2	0.9931	0.9103	0.9274	0.7677

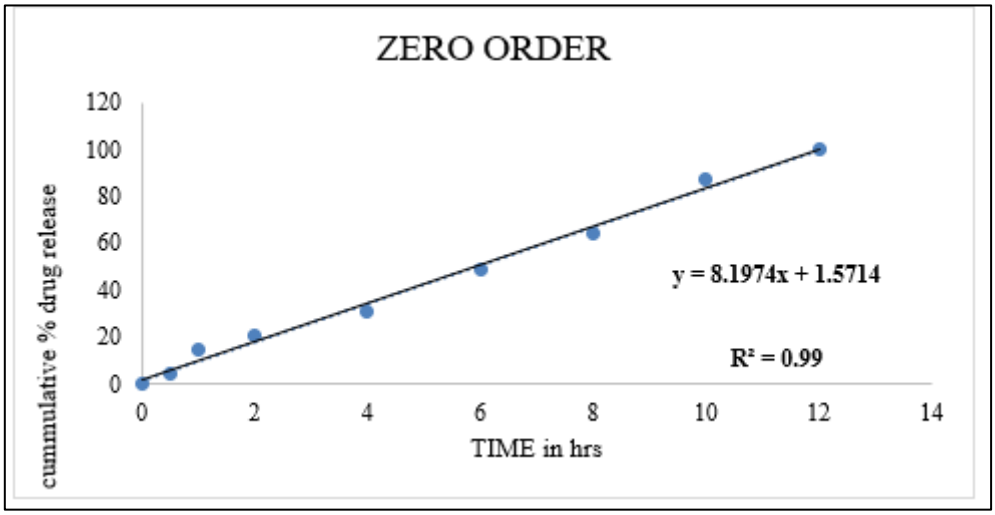

Fig 13: The zero-order release profile of bilayer tablets of the best formulation

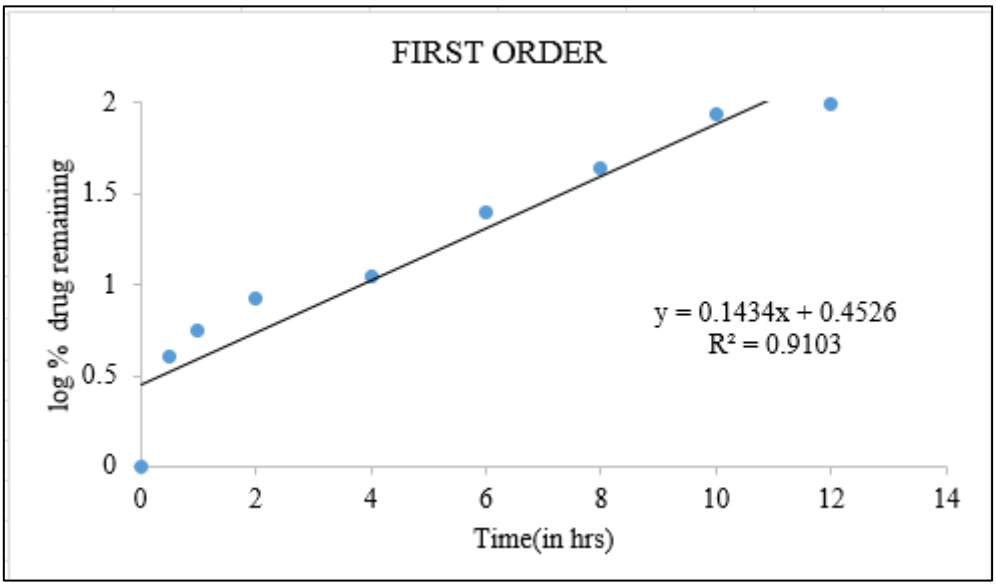

Fig 14: The first-order release profile of bilayer tablets of the best formulation

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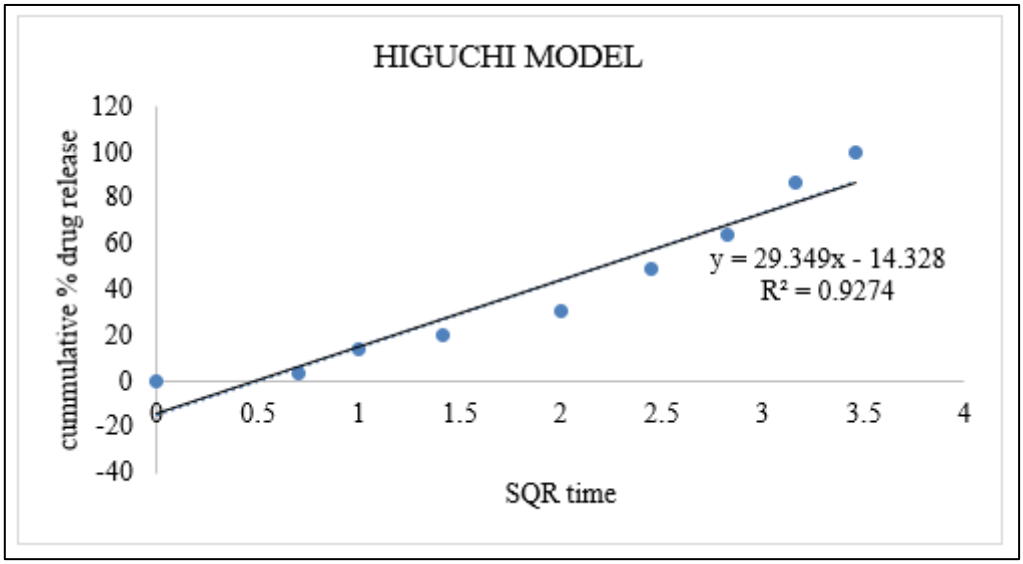

Fig 15: Higuchi releases kinetics profile of bilayer tablets' best formulation

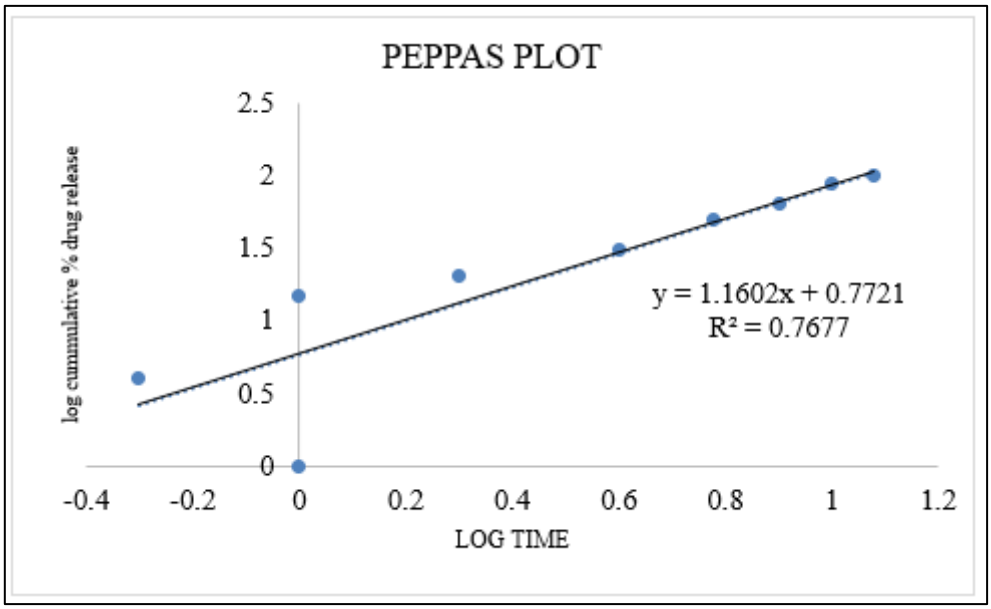

Fig 16: Peppas release kinetics profile of bilayer tablets of the best formulation

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10. Stability Studies Of The Optimized Formulation

Table 27

SNO	Time In hrs	Initial	Cumulative % drug release (mean SD) (n=3)								
			25±2°C,60±5%RH			30±2°C,65±5%RH			40±2°C,75±5%RH		
			1st month	2nd month	3rd month	1st month	2nd month	3rd month	1st month	2nd month	3rd month
Deferiprone IR layer											
1	0.25	77.5	77.7	77.6	77.5	77.5	77.8	77.5	77.5	77.6	77.5
2	0.5	100.3	100.3	100.2	100.1	100.3	100.1	100.2	100.3	100.3	100.2
Domperidone SR layer											
1	0.5	4.00	4.01	4.00	4.00	4.00	4.01	4.00	4.00	4.02	4.00
2	1	14.64	14.64	14.62	14.60	14.64	14.59	14.59	14.64	14.57	14.55
3	2	20.47	20.47	20.46	20.43	20.47	20.42	20.40	20.47	20.40	20.40
4	4	30.99	30.99	30.99	30.98	30.99	30.98	30.97	30.99	30.95	30.95
5	6	49.13	49.13	49.11	49.11	49.13	49.10	49.10	49.13	49.05	49.05
6	8	64.26	64.26	64.26	64.25	64.26	64.25	64.24	64.26	64.22	64.21
7	10	87.41	87.41	87.41	87.40	87.41	87.40	87.39	87.41	87.35	87.34
8	12	99.83	99.83	99.83	99.82	99.83	99.81	99.80	99.83	99.78	99.76

Table 28: Stability Studies for post compression parameters of Optimised Bilayer Tablet

SNO	parameters	Initial	Cumulative % drug release (mean SD) (n=3)								
			25±2°C,60±5%RH			30±2°C,65±5%RH			40±2°C,75±5%RH		
			1st month	2nd month	3rd month	1st month	2nd month	3rd month	1st month	2nd month	3rd month
1	**Average weight(mg)**	**800**	800	800	800	800	800	749	800	749	800
2	**Thickness (mm)**	**2.9**	2.9	2.9	2.9	2.9	2.9	2.8	2.9	2.8	2.7
3	**Hardness (Kg/cm2)**	**6.4**	6.4	6.4	6.4	6.4	6.3	6.3	6.4	6.1	6.1
4	**Friability (%)**	**0.55**	0.55	0.55	0.55	0.55	0.54	0.54	0.55	0.49	0.48

CONCLUSION

The goal of the research was to develop and evaluate a bilayer tablet that contained domperidone and deferiprone. Domperidone and Deferiprone were more soluble in 0.1N HCL, according to pre-formulation experiments. The absorption maxima of deferiprone and domperidone, respectively, were 278 nm and 230 nm, indicating that the medicine and excipients did not interact, according to FTIR analysis. Following optimization, the Deferiprone immediate release formulation F6 showed an acceptable average weight variation of 650, average thickness of 2.92, average hardness of 6.24, average friability of 0.55, disintegration time of 20 seconds, and drug content of 100.3. The improved formulation of Domperidone sustained release D3 demonstrated good average weight variation (150), average thickness (2.89), average hardness (6.1), average friability (0.59), and average drug content (99.83). The

drug release percentages for deferiprone and domperidone were determined to be 100.3% and 99.83%, respectively, indicating good content homogeneity. The optimal formulation of the drug release data demonstrated the best fit into First-Order Kinetics and the Higuchi model of Kinetics The improved formulation was the subject of a Dissolution investigation and showed better results of dissolution than the formulation without SLS. The formula showed good stability, and the values fell within the range. We conclude that bi-layered tablets containing deferiprone for instant release and domperidone for extended release can be used to generate stable dosage forms.

REFERENCES

1. Patel Pinkesh[*1], Patel Chirag J[1], Prof. Satyanand Tyagi[2], Umesh Kumar[1], Patel Jaimin[1], Chaudhari Bharat[1] "NOVEL APPROACH OF BILAYERED TABLETS: AN OVERVIEW" Pharma tutor edu labs, Pharmacy infopedia 20 December 2012
2. Ansel .2006. 'Pharmaceutical dosage forms & drug delivery systems-Types of tablets'. 8th Edition, 227-260.
3. Sarvesh D Parsekar*, Shruti Prabhu, Amitha Shetty, Mohd Azharuddin and AR. Shabaraya Floating Bilayer Tablet as a Convenient Gastroretentive Drug Delivery System.
4. https://www.nhlbi.nih.gov/health/thalassemia
5. https://www.nhlbi.nih.gov/health/thalassemia/symptoms
6. https://www.nhlbi.nih.gov/health/thalassemia/causes
7. Foong, Wai Cheng; Loh, C Khai; Ho, Jacqueline J; Lau, Doris SC (13 January 2023). Cochrane Cystic Fibrosis and Genetic Disorders Group (ed.). "Foetal haemoglobin inducers for reducing blood transfusion in non-transfusion-dependent beta-thalassaemias". *Cochrane* 2023 (1):CD013767. doi:10.1002/14651858.CD013767.pub2. PMC 9837847. PMID 36637054.
8. Tintinalli, Judith E. (2010). *Emergency Medicine: A Comprehensive Study Guide (Emergency Medicine (Tintinalli))*. New York: McGraw-Hill Companies. p. 830. ISBN 978-0-07-148480-0.
9. V P Choudhry [1]and all ".Deferiprone, efficacy and safety" Pubmed: Indian JPediatr 2004 Mar;71(3):213-6. PMID: 15080407, doi: 10.1007/BF02724272.
10. Vip Viprakasit and all "Deferiprone (GPO-L-ONE(®)) monotherapy reduce iron overload in transfusion-dependent thalassemias: 1-year results from a multicenter prospective, single-arm, open-label, dose-escalating phase III pediatric study (GPO-L-ONE; A001) from Thailand", Am J Hematol 2013 Apr;88(4):251-60. PMID: 23460233 , doi: 10.1002/ajh.23386. Epub 2013 Mar 5.
11. Ampaiwan Chuansumrit et al, "The safety profile of a liquid formulation of deferiprone in young children with transfusion-induced iron overload: a 1-year experience", Paediatr Int Child Health 2016 Aug;36(3):209-13. PMID: 26052612doi: 10.1179/2046905515Y.0000000040.
12. Maria Marsella et al , "Transfusional iron overload and iron chelation therapy in thalassemia major and sickle cell disease", Hematol Oncol Clin North Am 2014 Aug;28(4):703-27, vi. PMID: 25064709 doi: 10.1016/j.hoc.2014.04.004.
13. A Victor Hoffbrand et al , "Deferiprone Therapy For Transfusional Iron Overload", Best Pract Res Clin Haematol 2005 Jun;18(2):299-317. Pmid: 15737892 Doi: 10.1016/J.Beha.2004.08.026.
14. Giuseppina Calvaruso et al, "Deferiprone Versus Deferoxamine In Thalassemia Intermedia: Results From A 5-Year Long-Term Italian Multicenter Randomized Clinical Trial", Am J Hematol 2015 Jul;90(7):634-8. Epub 2015 May 3. Pmid: 25809173 Doi: 10.1002/Ajh.24024
15. Shau-Yin Ha et al, "A Randomized Controlled Study Evaluating The Safety And Efficacy Of Deferiprone Treatment In Thalassemia Major Patients From Hong Kong", Hemoglobin 2006;30(2):263-74.Pmid: 16798652 Doi: 10.1080/03630260600642617
16. Robert C. Hider et al, "The Role Of Deferiprone In Iron Chelation ", November 29, 2018, N Engl J Med 2018; 379:2140-2150, Doi: 10.1056/Nejmra1800219
17. Moshen S Elalfy et al,"The Safety, Tolerability, And Efficacy Of A Liquid Formulation Of Deferiprone In Young Children With Transfusional Iron Overload", J Pediatr Hematol Oncol. 2011 Oct;33(7):572. PMID: 20921906
Doi: 10.1097/MPH.0b013e3181ec0f13.
18. Vasilios Berdoukas et al, Treating Thalassemia Major-Related Iron Overload: The Role Of Deferiprone", J Blood Med. 2012; 3: 119–129
19. Chaim Hershko et al, "Objectives And Mechanism Of Iron Chelation Therapy"-Pubmed Ann N Y Acad Sci 2005:1054:124-35.Pmid: 16339658, Doi: 10.1196/Annals.1345.015
20. Chaim M Hershko et al, "Iron Chelation Therapy"-Pubmed Curr Hematol Rep 2005 Mar;4(2):110-6. Pmid: 15720959
21. Amal El-Beshlawy et al, "Iron Chelation In Thalassemia: Combined Or Monotherapy? The Egyptian Experience"-Pubmed Ann Hematol 2008 Jul;87(7):545-50. Doi: 10.1007/S00277-008-0471-2. Epub 2008 Mar 20. Pmid: 18351337 Doi: 10.1007/S00277-008-0471-2
22. Mikhael Yosia et al,-"A Side Effect Of Deferiprone As An Iron Chelator In Children With Thalassemia "-Paediatrica Indonesiana Vol 57 No 6 (2017): November 2017
23. Tanya Ramados et al, "Topical Iron Chelator Therapy: Current Status and Future Prospects"-October 2023 Cureus 15(10), DOI:10.7759/cureus.47720, License CC BY 3.0

24. Bernard Charles Sherman et al, "Delayed Release Deferiprone Tablets And Methods Of Using The Same"-United States Patent Sherman Et Al . , Patent No .: Us 10,780,055 B2,- Date Of Patent : * Sep . 22, 2020
25. Michael Spino et al, "Liquid Formulation For Deferiprone With Palatable Taste"-United States US 2011 0039897a1, Patent Application Publication, Pub. No.: Us 2011/0039897 A1 Spino Et Al., Pub. Date: Feb. 17, 2011
26. Savio C Reddymasu et al, "Domperidone: Review Of Pharmacology And Clinical Applications In Gastroenterology"-Am J Gastroenterol. 2007 Sep;102(9):2036-45., Epub 2007 May 3
27. Naveed Ahmad et al,"Making a case for domperidone in the treatment of gastrointestinal motility disorders"-Curr Opin Pharmacol, 2006 Dec;6(6):571-6., Epub 2006 Sep 25.
28. Savita Shahani et al, "Rabeprazole Plus Domperidone: The Answer For Gastro-Oesophageal Reflux Disease"-J Indian Med Assoc, 2008 Apr;106(4):264, 266, 268.
29. Prof.Parbhane M.B. et al. "Antacid Bilayer Tablet Formulation (Rabeprazole And Domperidone)"-International Journal Of Creative Research Thoughts (Ijcrt) Volume 11,12 December 2023
30. Chen Ying et al,"Method Of Preparation Of Domperidone Tablet "-Worldwide Applications 2014 J E Valenzuela et al, "Dopamine Antagonists In The Upper Gastrointestinal Tract"-Scand J Gastroenterol Suppl 1984:96:127-36.
31. Dr Y. Krishna Reddy et al, "Formulation And Evaluation Of Effervescent Floating Tablets Of Domperidone"-Asian Journal Of Research In Pharmaceutical Sciences (Ajpsci)Volume - 10, Issue - 1, Year - 2020
32. V. Vijayan et al, "Design And Evaluation Of Domperidone Once Daily Sustained Release Matrix Tablets"-Journal Of Chemical And Pharmaceutical Sciences. Volume-1 Issue-2 October - December'2008
33. Swati Saxena et al, "Formulation And Evaluation Of Bilayer Tablet: A Review"- International Journal Of Creative Research Thoughts Issn:2320-2882
34. Mounika Chidurala1 Orcid et al, "Design And Characterization Of Combinational Domperidone-Famotidine Floating Drug Delivery System - In Vitro And In Vivo Studies"-ARS PHARMACEUTICALS 22.03.2021
35. Jessica Cha et al. "12 - Stability Studies"- Separation Science and Technology Volume 10, 2011, Pages 459-505
36. Hammad Ahmed et al, " Methods And Protocols For Drug Stability Studies"-Drug Stability And Chemical Kinetics First Online: 02 November 2020
37. https://go.drugbank.com/drugs/DB08826
38. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208030s002lbl.pdf
39. https://go.drugbank.com/drugs/DB01184
40. https://www.drugs.com/domperidone.html

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