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DEVELOPMENT AND EVALUATION OF DOMPERIDONE SUSTAINED RELEASE MATRIX TABLETS USING *Hibiscus rosa-sinensis* LEAVES MUCILAGE

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Abstract:

Domperidone, a peripherally selective dopamine D2 receptor antagonist, is utilized for its anti-emetic, gastroprokinetic, and galactogogue properties. Despite being poorly soluble in water, it is classified as a Class II drug under the Biopharmaceutics Classification System. Formulation studies using natural polymer ratios led to the identification of an optimized formulation (F3) for sustained release. FTIR analysis confirmed compatibility within the formulations. Utilizing *Hibiscus rosa-sinensis* leaves mucilage as a natural polymer showed promise in enhancing drug bioavailability and sustaining release, making it a viable option for oral delivery systems. This study highlights the potential of natural polymers in improving drug dissolution and patient compliance in therapy.

Key Words: Domperidone, anti-emetic, gastroprokinetic, galactogogue, *Hibiscus rosa-sinensis* leaves mucilage, drug bioavailability, oral delivery systems, patient compliance.

INTRODUCTION:

SUSTAINED RELEASE DRUG DELIVERY:

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body. Sustained release (SR) preparations are not new but several new modifications are being introduced. They are also referred to as “Long acting” or “Delayed release” when compared to “rapid” or “conventional” release preparations. The term sometimes overlaps with “Controlled release,” which implies more sophisticated control of release and not just confined to the time dimension.

DOMPERIDONE:

- Domperidone shows gastro prokinetic and anti-emetic activity and used in themanagement of upper GIT motility and gastro paresis by blocking Dopamine (D2)receptors at chemoreceptor trigger zone in postrema and also at the gastric region.
- When administered as conventional tablet dosage form, its onset of action is about 30minutes and the drug produces its effect for 4-7 hours. Drug release studies of theseimmediate release tablet dosage forms in healthy subjects.

- Domperidone were not detectable in blood after few hours of oral administration andeliminated in 5-7 hours from the body.

The aim of our study was to prepare sustained release Domperidone matrix tablets usingnatural polymers like *Hibiscus rosa-sinensis* leaves mucilage to reduce the frequency ofconventional dosage form, side effects and also to show the effect of concentration ofpolymers used on release kinetics for the matrix tablet.

***Hibiscus rosa-sinensis* LEAVES**:

Hibiscus rosa-sinensis is a bushy, ever green shrub or small tree growing 2.5 to 5 cm tall

and 1.5 to 3 m wide with glossy leaves and solitary, brilliant red flowers in summer.

SCIENTIFIC CLASSIFICATION:

Kingdom : Plantae

Order : Malvales

Family : Malvaceae

Genus : Hibiscus

Species : *Hibiscus rosa-sinensis*

CRITERIA FOR SUSTAINED RELEASE DRUG DELIVERY SYSTEM

Physico-chemical parameters for drug selection:

- Molecular weight/size < 1000 Daltons.
- Solubility > 0.1 mg/ml for pH 1 to pH 7.8.
- Apparent partition coefficient High.
- Absorption mechanism Diffusion.
- General absorbability from all GI segments.

Release should not be influenced by pH and enzymes

TECHNIQUES FOR PREPARING SUSTAINED RELEASE MATRIX TABLETS

The therapeutic index also factors whether a drug can be used as a time release drug. A drug with a thin therapeutic range, or small therapeutic index, will be determined unfit for a sustained release mechanism in partial fear of dose dumping which can prove fatal at the conditions mentioned. For a drug that is made to be released over time, the general goals are to stay within the therapeutic range as long as needed.

There are many different methods used to obtain a sustained release:

- Diffusion systems
- Dissolution systems
- Osmotic systems
- Ion-exchange resin
- Floating systems
- Bio-adhesive systems
- Matrix systems

MATRIX TABLETS:

- For the manufacturing of sustained release dosage forms least complicated method involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix core of the retardant.
- Alternatively drug and retardant blend may be granulated prior to compression.
- The materials which include both hydrophilic and hydrophobic polymers. Matrix tablet generally classified into different types:

a) Hydrophilic Matrix Tablet

1) Cellulose derivatives
2) Non-cellulose natural or Semi-synthetic polymers
3) Acrylic acid polymer

b) Plastic Matrix Tablet (Hydrophobic matrices)

MATERIALS AND METHODS

Drug of choice to prepare sustain release matrix tablets is Domperidone, based on available information of Domperidone; no work was carried out on sustained release matrix tablets of Domperidone with *Hibiscus rosa-sinensis* leaves mucilage, so we planned to carry out on Domperidone using excipients like Microcrystalline cellulose, Magnesium stearate , Talc, *Hibiscus rosa-sinensis* leaves mucilage.

METHODOLOGY:

Procedure:

STEP 1: Preparation of *Hibiscus rosa-sinensis* leaves Mucilage.

STEP 2: Preparation of Granules.

STEP 3: Preparation of Matrix Tablets.

PREPARATION OF *Hibscus rosa-sinensis* LEAVES MUCILAGE:

STEP 1: Fresh leaves were collected and washed with water.

STEP 2: The leaves were then crushed and then kept were soaking for 5 to 6 hours.

STEP 3: The leaves were boiled for 30 minutes and left to stand for 1 hour for complete release of mucilage.

STEP 4: The mucilage was extracted using a muslin cloth bag to remove the marc from the solution.

STEP 5: Acetone (3times the volume of filtrate) was added to precipitate the mucilage.

STEP 6: The mucilage was separated dried in an oven at 35ºc collected, grounded, passed through sieve no.40 and stored in a Desiccator at 35^0c and 45% relative humidity till use**.**

PREPARATION OF GRANULES AND MATRIX TABLETS:

- The extracted mucilage of *Hibiscus rosa-sinensis* was studied for the desired physical properties.
- Matrix tablet each containing 100 mg of Domperidone were prepared using dried mucilage of *Hibiscus rosa- sinensis* leaves in various ratio of 1:0.15, 1:0.3, 1:0.45. (Drug: Mucilage).

- The active ingredient Domperidone, bio-polymers (*Hibiscus rosa-sinensis* leaves mucilage), diluents and fillers except lubricants and glidants were mixed properly in a laboratory scale for 15 minutes after passing them through a suitable mesh until a uniform mixture was obtained.
- Then water was slowly added at a steady rate to the blended material and mixed well to get a uniform wet mass that was passed through mesh number 10 and dried in a tray dryer at 45-60 ° C for 1 hour.
- The dried granules were then passed through the mesh number 22.
- The dried granules were lubricated with Magnesium Stearate mixing in polythene bag.
- Various formulations of Domperidone matrix tablets were prepared by Wet granulation technique.

Finally, granules were compressed at a compression force of 6500-7500.Tablet compression machine using 6.0 mm diameter, Edge punches.

Table No. 1.1: Formula for Matrix Tablets of Domperidone

NAME OF THE INGREDIENTS	F1(mg)	F2(mg)	F3(mg)
Domperidone	100	100	100
***Hibiscus rosa-sinensis* leaves Mucilage**	15	30	45
Microcrystalline Cellulose (Avicel)	130	115	145
Magnesium Stearate	5	5	5
Total Tablet weight	250	250	250

***In vitro* EVALUATION TESTS**

- Weight variation test
- Drug content
- Hardness
- Friability
- Disintegration test
- Dissolution studies
- Swelling index

RESULTS AND DISCUSSION

- The extracted mucilage of *Hibiscus rosa-sinensis* was studied for the desired physical properties. Matrix tablets each containing 100

- mg of Domperidone were prepared using dried mucilage of *Hibiscus rosa-sinensis* leaves in various ratios of 1:0.15, 1:0.3, 1:0.45 (Drug: Mucilage**).**

- **Calibration curve of Domperidone:**

Table no. 1.2 : Calibration curve of Domperidone

S.No.	Concentration (µg/ml)	Absorbance at 285 nm
1	0	0
2	5	0.043
3	10	0.081
4	15	0.118
5	20	0.155
6	25	0.193

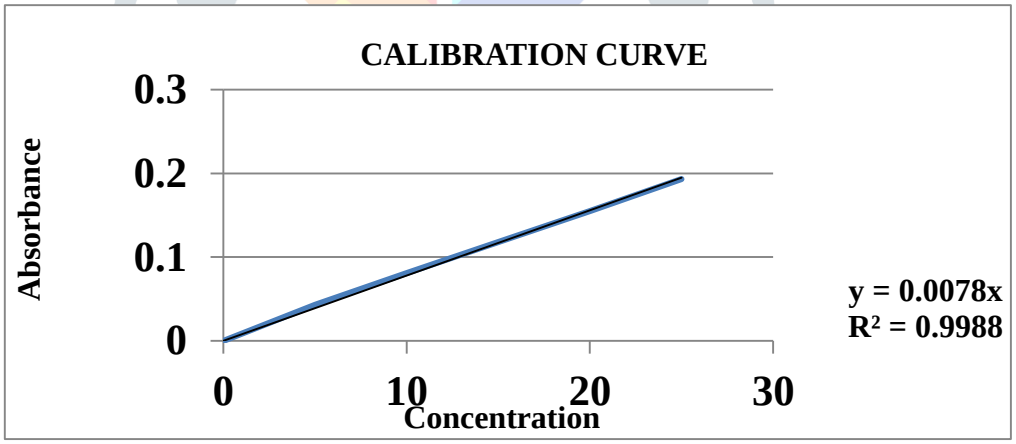

Fig.no:1.1 Calibration Curve of Domperidone in pH 6.8 phosphate buffer

- **Evaluation of Pre-compression parameters:**

Table No. 1.3: The results of Pre-compression studies were given in the below table

Formulation	Angle of Repose(Ɵ)(degrees)	Bulk density(gm /ml)	Tapped density(gm/ml)	Carr's index[%]	Hausner's ratio
F1	17.2±0.05	0.40±0.002	0.70±0.003	42.90±0.2	1.75±0.04
F2	18.2±0.04	0.55±0.003	0.82±0.004	32.90±0.3	1.49±0.02
F3	18.5±0.06	0.80±0.005	0.92±0.006	13.00±0.3	1.15±0.05

- ***In vitro* Evaluation tests of Post-compression parameters:**

Table No. 1.4: Evaluation tests of Post-compression parameters

Formulation	Thickness (mm)	Weight Variation (%)	Hardness (kg/cm^2)	Friability (%)	Disintegration Time(min.)	Drug content (%)
F1	3.64	0.896±0.05	4-6	2.00±0.04	7mins 53secs	92
F2	3.70	0.960±0.15	4-6	1.00±0.12	8mins 59secs	95
F3	3.75	1.080±0.08	4-6	0.50±0.14	12mins 45secs	99

- **Swelling Index:**

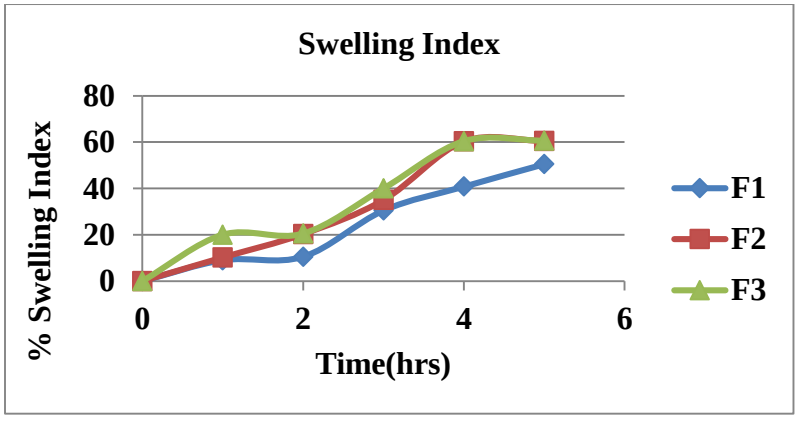

Fig.no:1.2 Swelling Index of different formulations

- Drug content was ranging from 92% to 99%.Swelling index for the formulations F1, F2 and F3 were found to be 50.5 %, 62.3% and 68% respectively. *In vitro* release profile of Domperidone matrix tablets showed sustained release pattern with the maximum release for formulation-3 for 8 hrs and considerable decline in drug with increase in mucilage concentration. Thus, with increased concentration of mucilage, drug release also increased.

- ***In vitro* Dissolution studies:**

Table No. 1.5: *In vitro* Dissolution Profile of Formulations F1-F3

S.No.	Time (hrs)	F1	F2	F3
1.	0	0	0	0
2.	1	65.10	70.16	72.24
3.	2	78.18	83.26	87.32
4.	3	87.20	88.39	91.42
5.	4	90.37	92.46	97.51
6.	5	92.48	95.57	98.64
7.	6	95.59	97.66	98.75
8.	7	96.68	98.79	99.86
9.	8	98.70	98.83	99.92

- **RELEASE KINETICS OF FORMULATIONS:**

Table. No: 1.6: Release Kinetics

Formulation	RELEASE KINETICS									
	Zero order		First order		Higuchi matrix		Peppas		Hixson Crowell	
	R^2	K	R^2	K	R^2	K	R^2	K	R^2	K

F1	0.595	9.0	0.851	-17.8	0.930	22.32	0.391	10.74	0.891	-3.74
F2	0.552	8.8	0.818	-17.3	0.952	21.26	0.379	10.38	0.763	-3.65
F3	0.517	8.6	0.791	-16.8	0.960	21.12	0.374	10.16	0.726	-3.50

- The *In vitro* drug release data were fitted to release kinetics. The predicted drug release mechanism by PCP Disso V3 software indicated that all the formulations showed R^2 value between 0.930 – 0.960.Formulation F3 showed R^2 value of 0.960 and k value of 21.12.This predicted that the drug release mechanism was by Matrix model where the drug release could be by diffusion process.

- ***In vitro* Drug release studies of three formulations (F1-F3):**

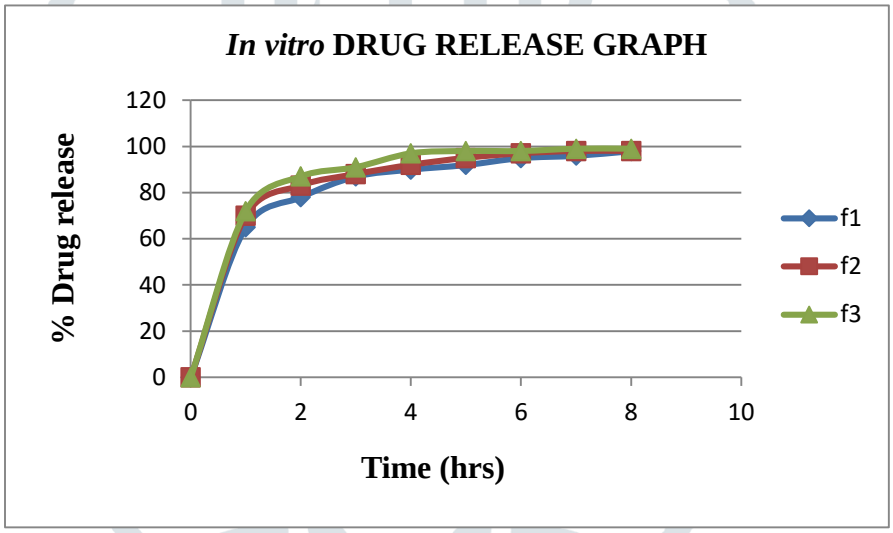

Fig. no:1.3: Dissolution Profiles of Domperidone Formulations (F1, F2 & F3) prepared with *Hibiscus rosa-sinensis* leaves mucilage

COMPARATIVE STUDIES OF GENERIC AND BRANDED DRUGS:

- Active ingredients are the same, the excipients (inactive ingredients) may differ. This is only important in rare cases when a patient has an allergy or sensitivity to one of the excipients.
- The product may also be slightly different in colour, shape or markings.
- The biggest difference is cost. Generic drugs are generally less expensive than brand name comparators

- **COMPARISON OF MARKETED DRUG VS F3 FORMULATION:**

Table. No: 1.7: Comparison of Marketed Product Vs Best Formulation (F3)

S.No.	Time (Hrs)	Pure Drug	Drug with Polymer Formulation (F3)
1.	0	0	0
2.	1	50.11	72.21
3.	2	66.26	87.33
4.	3	75.31	91.46
5.	4	82.45	97.50
6.	5	88.53	98.67
7.	6	90.67	98.74
8.	7	94.70	99.81
9.	8	96.86	99.93

- **Comparative Dissolution profiles of Domperidone with Best formulation (F3)**

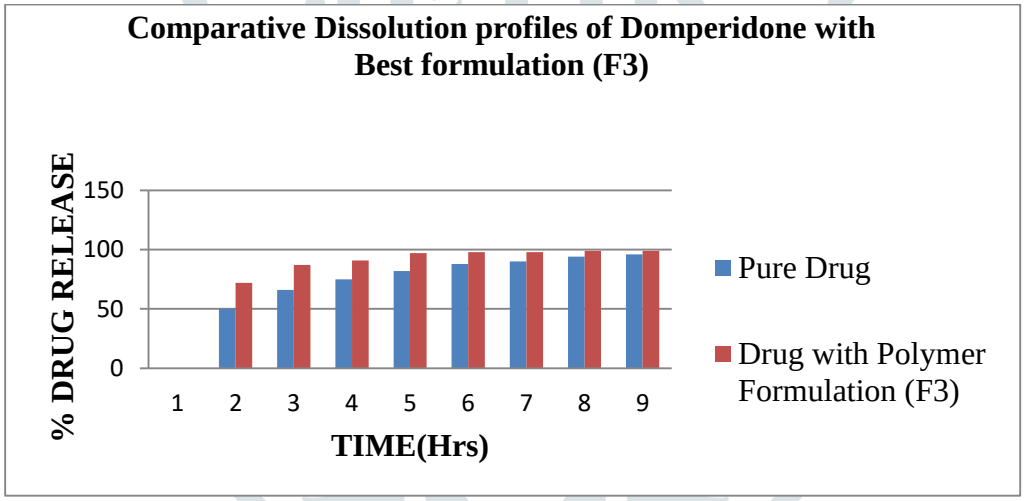

Fig.no:1.4 Comparative Dissolution profiles of Domperidone with Best formulation (F3)

- The drug release of marketed drug (Domperidone) was compared with the best formulation (F3).
- The marketed drug shows 96% of drug release where as Domperidone formulated with *Hibiscus rosa-sinensis* leaves mucilage showed 99%of drug release.
- As Domperidone drug is poorly soluble when formulated with *Hibiscus rosa-sinensis* as a natural polymer it increased the solubility by 4% and hence the bioavailability also increases.
- Therefore the patient compliance also becomes easier.

Incompatibility studies by FTIR spectra:

- Fourier – transfer infrared spectroscopy (FTIR) is a technique used to obtain an infrared spectrum of absorption or emission of a solid, liquid and gas.

- An FTIR spectrometer simultaneously collects high – spectral – resolution data over a wide spectral range.
- This confers a significant advantage over a dispersive spectrometer, which measures intensity over a narrow range of wavelengths at a time.
- In this FTIR studies reveals that there are no incompatibilities among the ingredients used in the Formulation.

- **FTIR spectra of Domperidone:**

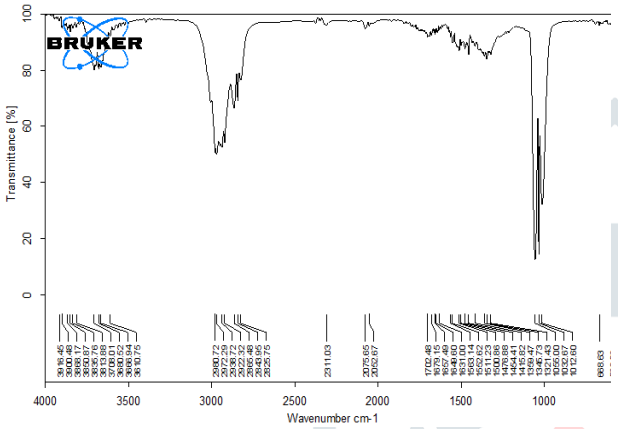

Fig.no:1.5 FTIR spectra of Domperidone

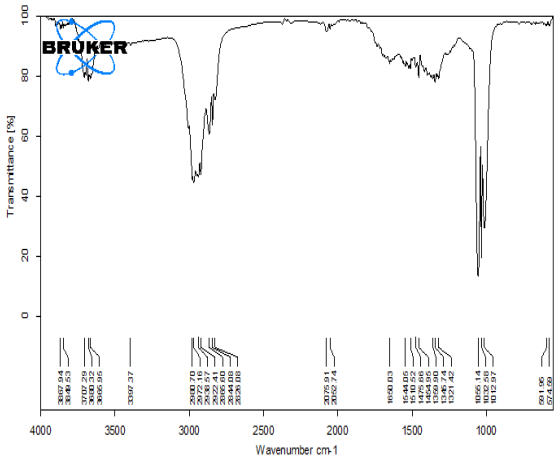

Fig.no:1.6 FTIR spectra of *Hibiscus rosa-sinensis* leaves mucilage

- **FTIR spectra of mixture of Domperidone and *Hibiscus rosa-sinensis* leaves mucilage:**

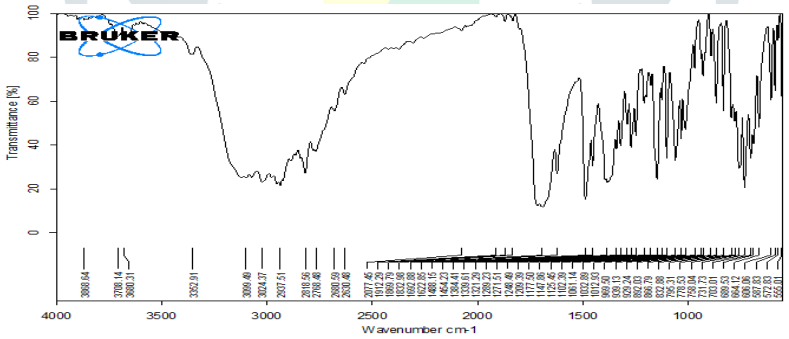

Fig.no:1.7 FTIR spectra of Domperidone and *Hibiscus rosa-sinensis* leaves mucilage

DISCUSSION:

All the formulations have shown Pre-formulation tests results within the limits. The formulations have shown the angle of repose in the range of 17.15° to 18.56° indicating Excellent flow. The Carr's index and Hausner's ratio were found to be in the range of 12.70% to 13.30% and 1.10 to 1.20 respectively indicating the good flow properties.

All the formulations have also passed the Post-compression parameters with weight variation ranging from 1.00% to 1.16% indicating that it is within the limits. Hardness was found to be in the range of 4 to 6kg/cm^2 and Friability in the range of 0.36% to 0.64% indicating that the results are within the limits. Disintegration was

found to be rapid with a range of 7mins 53secs to 12 mins 45 secs. FTIR studies revealed that there are no incompatibilities among the ingredients used in formulation.

Based on the *In vitro* dissolution studies, the following interpretation was done:

- Formulations, F1 to F3 containing *Hibiscus rosa-sinensis* leaves mucilage as natural polymer shown 92, 95 and 99% drug content release respectively in 8hrs.

Results of *In vitro* drug release also revealed that, as the concentration of natural polymer increases cumulative percent of drug release was also significantly increases. Formulation F1 and F2 showed less drug release when compared to formulation F3.Based upon the results of *In vitro* drug release results formulation F3 was considered as optimized formulation.

SUMMARY AND CONCLUSION:

Sustained release matrix tablets of Domperidone with *Hibiscus rosa-sinensis* leaves mucilage could be considered as safe and useful oral delivery system to increase the drug bioavailability and to improve patient compliance. The mucilage exhibited an appreciable physicochemical properties and suited best for the development of sustained release tablets as indicated by the drug release studies. This can be used as a potential natural source over the synthetic release retardant. Hence, *Hibiscus rosa-sinensis* could be employed as a release rate retardant for sustaining the drug release from the formulation. The study leads us to conclude that *Hibiscus rosa-sinensis* leaves mucilage can be successfully used as natural polymer. Thus natural polymer exhibits Sustained release drug dissolution and improved bioavailability, thereby helping in effective therapy and improved patient compliance.

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