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Preparation and Evaluation of Mucoadhesive Microspheres of Domperidone Using Moringa Leaf Powder as Mucoadhesive Polymer

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ABSTRACT:
Objective: To prepare and evaluate the mucoadhesive microspheres of domperidone using Hydroxy propylmethylcellulose and Moringa leaf powder as mucoadhesive polymers.
Methods : Moringa leaf powder obtained from the leaves and preformulation studies were done. complexation with cyclodextrins was done to enhance the solubility of domperidone.The solid dispersions were used to prepare microspheres.
A five formulations of Domperidone microspheres were prepared by ionic gelation method. The moringa leaf powder and HPMC grades(100,15) were used as mucoadhesive polymers in different ratios to prepare Microspheres. In F1 HPMCK100 and in F2 HPMC K15 and F3 to F5 the concentration of leaf powder incresd from 100 to 250mg. The microspheres evaluated for various parameters %yield,Drug entrapment efficiency,In vitro wash off test to measure the mucoadhesive strength of microspheres and dissolution studies to know the drug release.
Conclusion:The work has concluded that microspheres of domperidone succesfuly formulated with moringa leaf powder and HPMC for sustained drug delivery. The work also concluded that the moringa leaf powder can be used as mucoadhesive polymer in sustained release dosage forms.
Key words: Muco adhesion,Microspheres, Cyclodextrins,Moringa leaf powder,Hydroxy propyl methyl cellulose and entrappment effeciency.

I.INTRODUCTION:

Now a days the use of natural polymers as pharmaceutical excepients was increased based on the factors like availability,safety and economical.These polymers can act as best substitutes for the synthetic ones in all aspects.

Moringa OleiferaLam. (Moringaceae) is one of the 14 species of the family moringaceae, native to India, Africa, Arabia, Southeast Asia, South America, and the Pacific and Caribbean Islands. Because M. oleiferahas been seen in many tropic and sub-tropic regions worldwide. The plant is referred to by a number of names such as horseradish tree, drumstick tree, ben oil tree, miracle tree, and "Mother's BestFriend". This plant grown and widely cultivated in the northern part of Nigeria and many countries in tropical Africa. Moeingaoleiferacanbe grown in a variety of soil conditions preferring well-drained sandy or loamy soilthat is slightly alkaline.

[1]Moringaas "natural nutrition for the tropics" Drumstick Leaves can be eaten fresh, cooked, or stored as dried powder for many months without refrigeration, and reportedly without loss of nutritional value. Moringais especially promising as a food source in the tropics because the tree is in full leafat the end of the dry season when other foods are typically scarce. A large number of reports on the nutritional qualities of Moringanow exist in both the scientific and the popularliterature. Moringa Oleiferacontain Vitamin A, calcium, iron, vitamin C and potassium respectively more than carrots, milk, spinach, oranges, and bananas. That the protein quality of Moringaleaves rivals that of milk and eggs. The leaves are rich in ironand therefore highly recommended for expectant mothers. Since allessential amino acids are present Moringa may be rightly called acomplete food for total nutrition.

DOM (domperidone) is a peripherally selective dopamine D2 receptor antagonist that is used as an antiemetic, gastroprokinetic agent and

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galactogue . Domperidone does not readily cross the blood brain barrier and hence is less likely to cause central nervous system effect like sedation and dystonic reactions. It acts at the CTZ (chemo receptor trigger zone) and is unlikely to be effective in motion sickness and other vestibular disorders. It has a low ceiling anti-emetic and pro-kinetic action.

[2]Drug release studies of immediate release dosage forms in healthy subjects shows that domperidone tablets were not detectable in blood after few hours of oral administration and is eliminated in 5-7 hours from the body . The dose of domperidone in adults greater than 16 is given as 10 mg 3 times daily. Microspheres of domperidone will provide constant and prolonged therapeutic effect, reduce dosing frequency and thereby improve the patient compliance. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effect and allow a controllable variability in degradation and drug release.

The aim of the present work was to sustain the drug release of domperidone by preparing mucoadhesive microspheres using HPMC and Moringa leaf powder as muco adhesive polymers to reduce the frequency of conventional dosage forms, side effects and improve adherence and health outcome.

II.MATERIALS

Materials : Domperidone, Lactose, Sodium Alginate, Hydroxy Propyl Methyl Cellulose, Calcium Chloride were purchased from yarrow chwmicals mumbai and moringa leaves collected from Tagarpuvalasa,Visakhapatnam.

III.EXPERIMENTAL METHODS:

Preparation of Moringa Leaf Powder:

The leaves were shade dried for two weeks and then pulverised using a blender. The leaves of moringa are collected from Moringa oliefera tree. Then the waste material including bark and the gum is separated. The resulting powders were stored in air tight containers.

Evaluation of Moringa Gum Powder

For the detection of the presence of carbohydrates, alkaloids, tannins, phenolic compounds, proteins standard tests for Moringa olifera powder were done and Flow properties of moringa leaf powder were done such as bulk density,tapped density, angle of repose and results were given in table no

Determination of pH:The pH of the leaf powder (1%w/v,2%w/v,3%w/v) was determined using a pH meter and results were given in table no

Construction of Standard curve of Domperidone

As domperidone is poorly soluble in water, organic solvent is required to solubilize the drug. The stock solution of domperidone 1mg/ml was prepared in ethanol and working standards (2,4,6,8,10µg/ml) were prepared by suitably diluting with 0.1 N HCl and the absorbance were measured using UV-Vis.Spectrophotometer at λ max 284 nm is against blank .

Formulation Of Mucoadhesive Microspheres Of Domperidone Using Moringa Leaf Powder

Preparation of inclusion complex

The solid complex of domperidone and β-cyclodextrin (βCD) (1:3molar ratio) was prepared by kneading method. Accurately weighed quantity of β-cyclodextrin was mixed with sufficient quantity of water to obtain a smooth and homogenous paste. Weighed quantity of domperidone along with citric acid was added slowly by grinding. The mixture was ground for one hour. Finally the paste was dried in hot air oven at 40 °C for 48 h. The dried complex was powdered and passed through sieve no. 100 and stored in airtight container till further use.

Preparation of sodium alginate microspheres

The appropriate amount of sodium alginate, HPMC K100M, HPMC K15, Moringa leaf powder, lactose, were dissolved in sufficient amount of distilled water and stirred for 20 min on the mechanical stirrer for complete swelling of polymers. Drug solution was slowly added to polymer solution with continuous stirring on the mechanical stirrer for 15 min. For the 10%calcium chloride solution, add 5 g of calcium chloride for every 100 ml of glacial acetic acid making sure to mix the solution well to dissolve the calcium chloride completely into glacial acetic acid . the 5% calcium chloride solution poured into a small bowl. a syringe was filled with mixture of Domperidone and sodium alginate solution. and microspheres prepared by putting drops from the syringe into the10%calcium chloride solution. Prepared mucoadhesive microspheres shown in figure 2.

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Table1:Formulation of Domperidone mucoadhesive microspheres

s.no	Ingredient	F1	F2	F3	F4	F5
1	Domperidone&β-cyclodextrin in 1:3(solid dispersion)	288 mg	288 mg	288 mg	288 mg	288 mg
2	Lactose	30 mg	30 mg	30 mg	30 mg	30 mg
3	Moringa leaf powder			100 mg	200 mg	250 mg
4	Hpmc k 100	200 mg	-	100 mg	-	-
5	Hpmc K15	-	200 mg	-	-	-
6	Sodium alginate	1gm	1gm	1gm	1gm	1gm
7	Glacial acetic acid	1 ml	1 ml	1 ml	1 ml	1 ml
8	Calcium chloride	5 gm	5 gm	5 gm	5 gm	5 gm
9	Distilled water	50 ml	50 ml	50 ml	50 ml	50 ml

EVALUATION OF DOMPERIDONE MICROSPHERES:

Percentage yield :

The yield of the prepared formulations was calculated as the percentage of the weight of the dried product at room temperature compared to the theoretical amount. Production yield is calculated using the following equation and reported in table 4.

Percentage yield = [weight of product/(weight of drug + other excipients)] × 100

Drug Entrapment Efficiency:

The microspheres (30 mg) loaded with domperidone solid dispersion was dissolved in solvent. drug were crushed and extracting with aliquots of 0.1N HCl repeatedly. The extract was transferred to a 100 mL volumetric flask and the volume was made up using 0.1N HCl. It was stirred for 6 hrs using magnetic stirrer. The resulting solution was then filtered and filtrate was suitably diluted with dissolution medium solvent. Domperidone content was determined spectrophotometrically at 284 nm from which entrapment efficiency was determined and reported in table 4.

Determination of particle size: The particle size of the microspheres was determined by using optical microscopy method. Approximately 100 mucoadhesive microspheres were counted for particle size determination and particle size was reported in table4.

In Vitro drug release study

Dissolution study of DOM and its microsphere formulations were performed in 900 ml of 0.1 N HCl using USP XXIII dissolution apparatus (Electrolab, TDT- 06P, Mumbai, India) for 6hrs under sink conditions at stirring speed of 100 rpm at 37±0.50C. Microspheres equivalent to 30mg domperidone was placed IN Paddle apparatus . 5 ml of aliquot was withdrawn at different time intervals and replaced with same volume of fresh dissolution medium. Filtered samples were assayed spectrophotometrically at 284 nm and reported table 8 an 9. 28

Measurment of mucoadhesive strength

Invitro wash off test:

The sheep mucosa was washed with physiological saline. After 15 min. the mucosa was held in inclined position and fixed to glass slide with cynoacrylate glue and 50 beads (N0) hydrated with little amount of water and dispersed on mucosal tissue and left on it for 20 min. for the interaction with mucosal surface. Then system was washed with 0.1 N HCl by using IV infusion set at the rate of about 22ml/min. After 20 min., 60 min, 120 min beads detached from the mucosa (Ns) were visually observed and percent mucoadhesion were calculated using following formula and shown in table 10 and figure 8.

% mucoadhesion strength = (N0 – Ns / N0) ×100

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IV.RESULTS

Table2:Physico chemical charecterization of Moringa leaf powder

Parameter	Result	Inference
Iodine test	Reddish brown ppt	Carbohydrates present
Ninhydrin test	Purple colour	Proteins present
Biuret test	Violet colour	Proteins present
Dragendroffs test	Violet colour	Alkaloids present
Tannins	Green	Tannins present
Flavanoids	Yellow to colour less	Flavanoids present

Table3:Flow properties and pH of Moringa leaf powder

Parameter	Value
Angle of repose	21.12
Bulk density	0.38 g/cc
Tapped density	0.5 g/cc
Carrs index	24
Hausners ratio	1.31
pH 1%w/v	6.59 ± 0.05
2%w/v	6.42 ± 0.04
3%w/v	6.37 ± 0.02

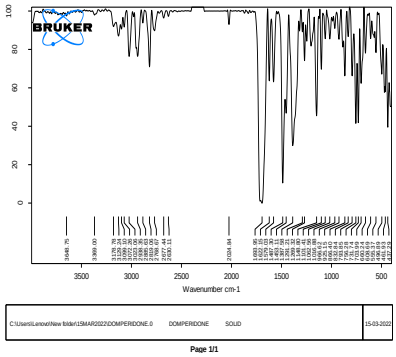

Fig1:FTIR of domperidone

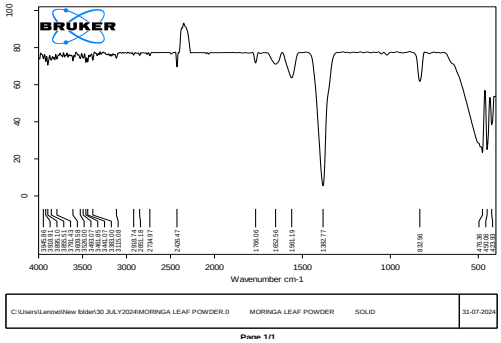

Fig2:FTIR of Moringa leaf powder

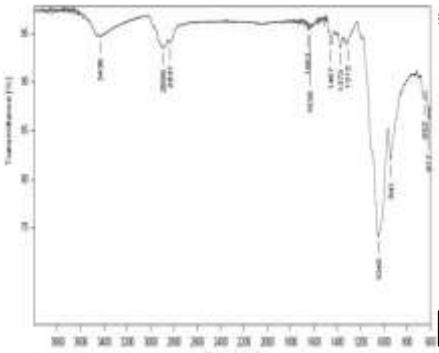

Fig3:FTIR of HPMC K15M

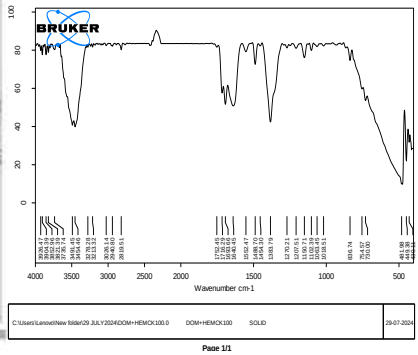

Fig4:FTIR of Domperidone and HPMC K100M

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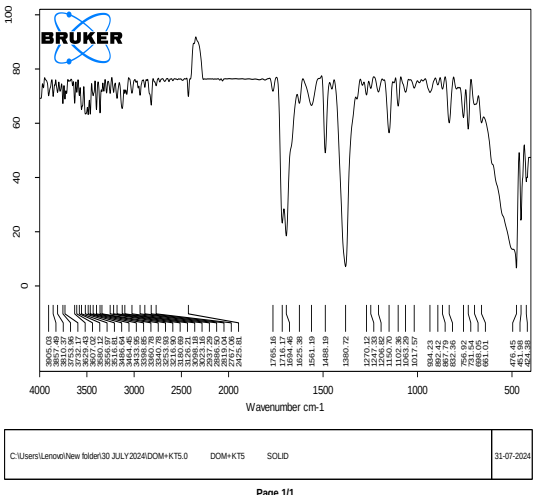

Fig5:FTIR of Domperidone and HPMCK15M

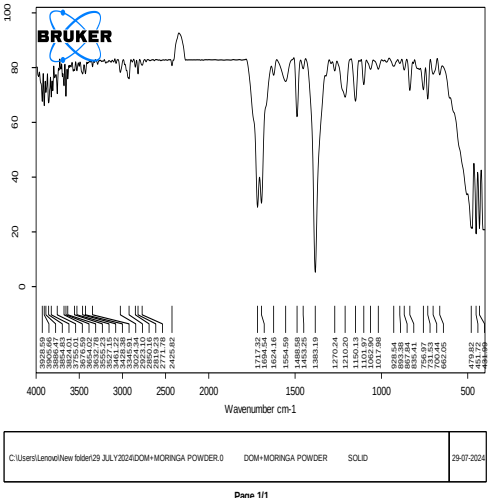

Fig6:FTIR of Domperidone and Moringa leaf powder

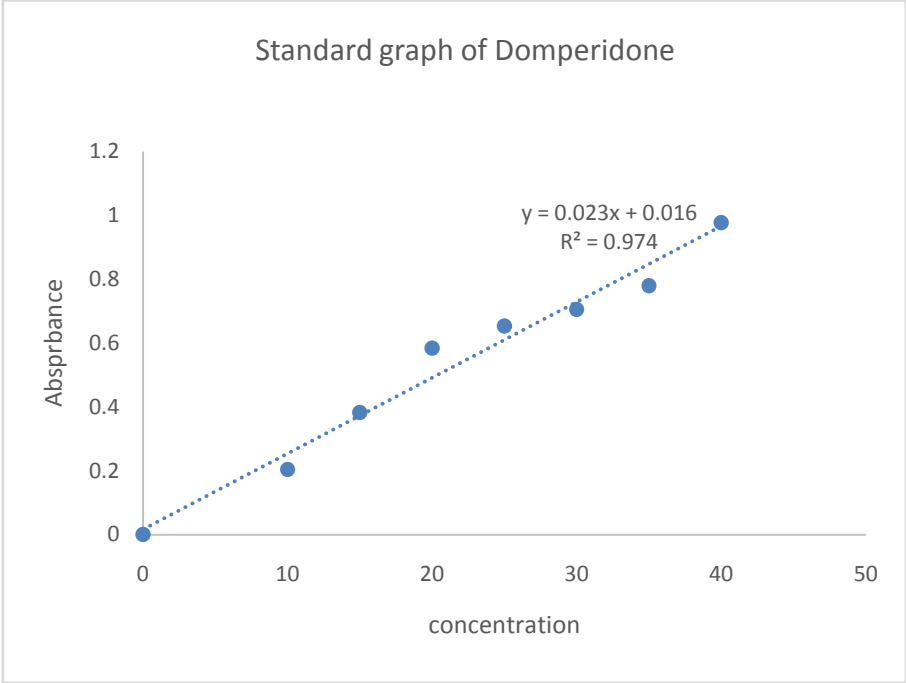

Fig7:Standard curve for Domperidone in 0.1N HCl

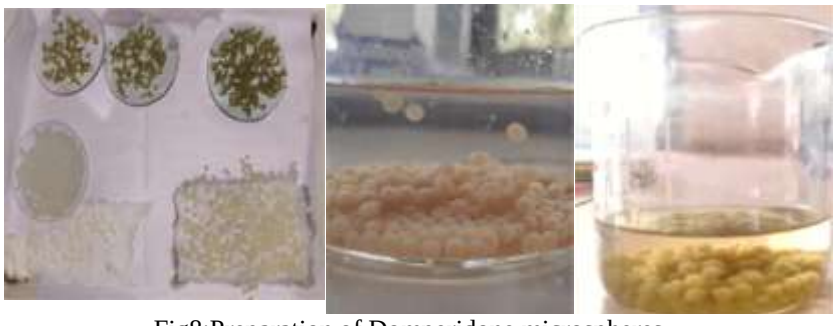

Fig8:Preparation of Domperidone microspheres

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Table4:Evaluation parameters for microspheres

Formulation	%yield	Particlesize	Drug entrapment effeciency
F1	35.61	567.6 µm	66.67%
F2	48.23	594.8 µm	51.76%
F3	55.63	499.7 µm	88.56%
F4	73.25	437.3 µm	86.66%
F5	69.24	547.5 µm	89.78%

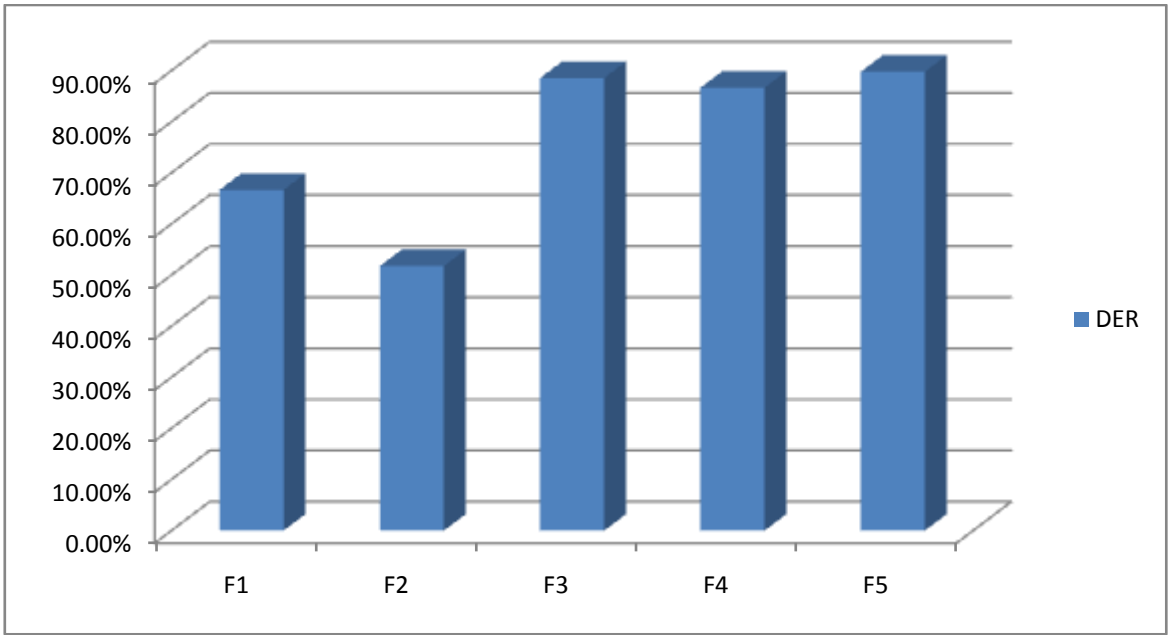

Fig9:Drug Entrappment Ratio

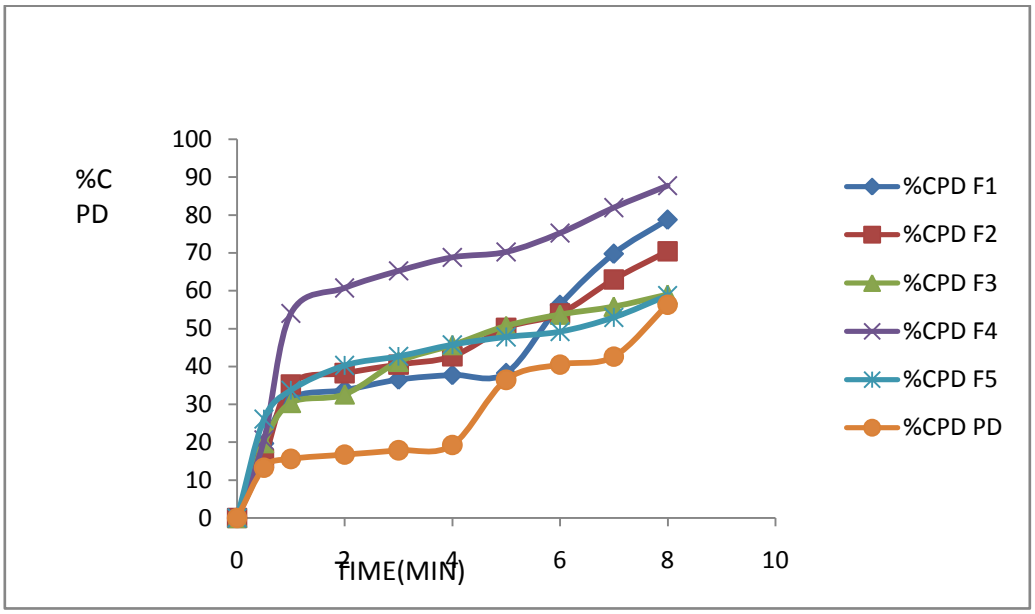

Fig10:Zero order curve (Cumulative percent drug release vs time)

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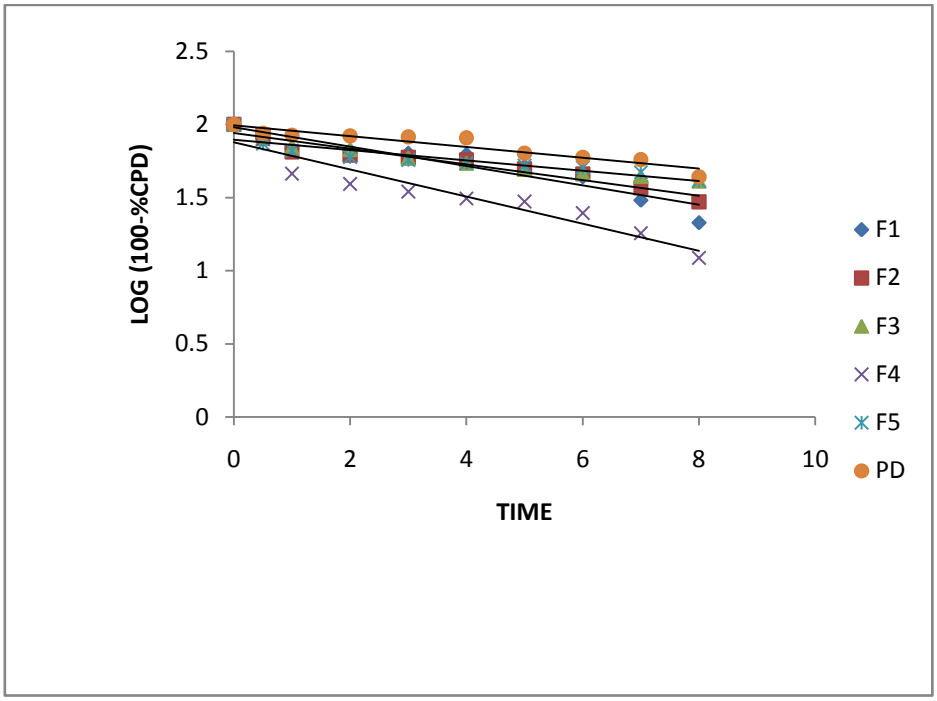

Fig11:First order curve(Log 5undissolved vs time)

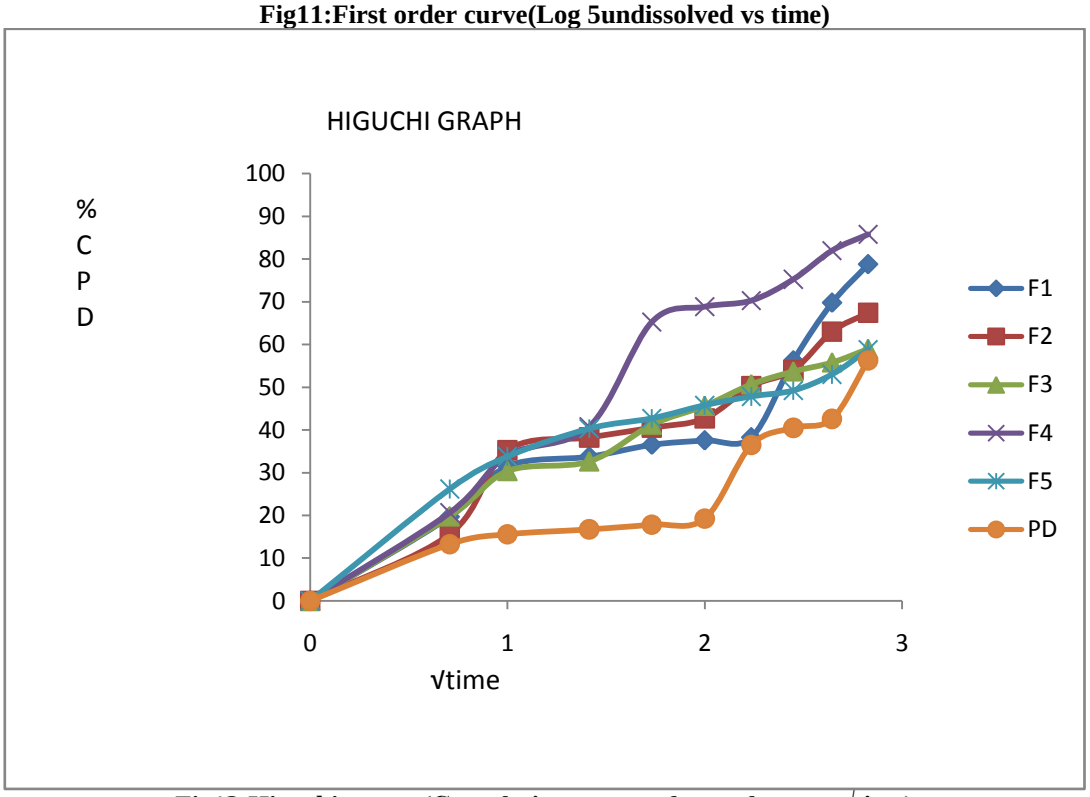

Fig12:Higuchi curve (Cumulative percent drug release vs √time)

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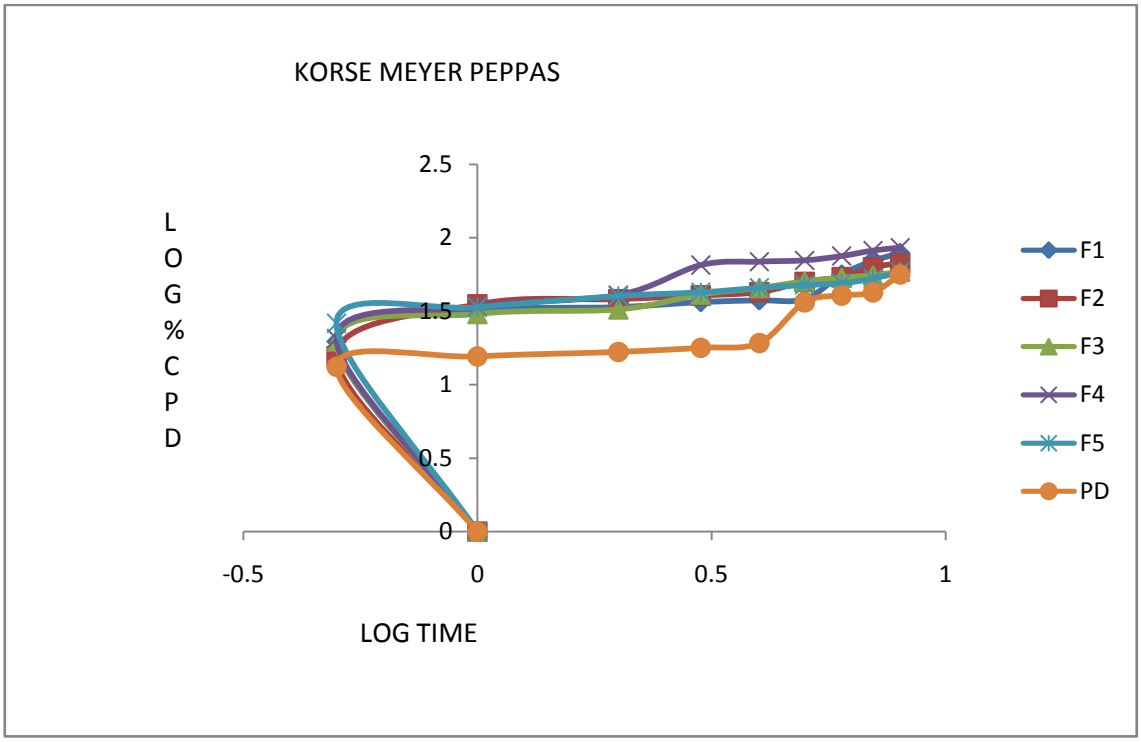

Fig13:Korsemeyer peppas curve

Table5: r^2 values of different pharmacokinetic models:

Order of kinetics					
	r^2 values				
	F1	F2	F3	F4	F5
Zero Order	0.779	0.8596	0.8454	0.7948	0.7324
First Order	0.848	0.929	0.921	0.919	0.837
Higuchi	0.9901	0.9935	0.9715	0.9715	0.955
Korsemeyer Peppas	0.511	0.462	0.4823	0.523	0.43
n values	1.18	1.123	1.13	1.293	1.604

Fig14:in-vitro wash off test of microspheres

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Table6:Results for in vitro wash off test

Time	F1	F2	F3	F4	F5
15min	83%	92%	87%	89%	95%
30min	72%	75%	78%	77%	87%
60min	53%	49%	62%	65%	69%
120min	45%	42%	43%	59%	57%

V.DISCUSIION:

Physico chemical properties were evaluated for moringa leaf powder and results were given in table no2.The flow properties were evaluated and results were given in table 3 and the powder has good flow properties.The pH of powder was measured and the values within the aceeptable range in table 3.

The FT-IR Studies were done for pure Domperidone powder and in combination with HPMC and Moringa leaf powder and the results has shown that there was no interaction between drug and excepients.The FTIR graphs were shown in figure nos 1 to6.

Calibration curve for domperidone was constructed in 0.1N HCl and shown in figure7 .The absorbance values increases with increase of concentration with r^2 value 0.974.

To increase the solubility of the domperidone inclusion complexes were prepared by kneading method. Domperidone and cyclodextrin were taken in 1:3 molar ratio.The powder was placed in air tight container till use.These solid dispersions were used for the preparation of mucoadhesive microspheres.In F1 and F2 HPMC K15 and HPMCK100 and for F3 to F5 moringa leaf powder was used by increasing the concentration as muco adhesive polymer.5 formulations were prepared by ionic gelation method.The composition was given in the table no 1. The formulations were shown in fig7 .

Percent yield was calculted and given in the table no4 and it was in the range of 30-70%. Drug entrapment effeciency for all the formulations were measured and it was in the range Particle size was measured by optical microscopy and results were given in the table no4 and particle size was in the range of 400-600µm. In vitro drug release studies were done by using dissolution apparatus and results were fitted into various kinetic models and r2 values given in the table no 5 based on r2 values the drug release follows first order in which drug release depends on concentration and drug release followed diffusion. Base on n vales of korse meyer peppas graph the diffusion followed supercase2 transport.

In vitro wash off test was done for all the microspheres by using goat mucosa and the results were given in the table6. The microspheres were attached to mucosa for several hours. Based on the results the formulations with moringa leaf powder has better muco adhesive properties.

VI.CONCLUSION:

In the present work Domperidone Muco adhesive microspheres was succesfully prepared by using HPMC and Moringa leaf powder by ionic gelation method. The microspheres has shown high drug encapsulation,Sustained drug release at controlled rate.Hence these microspheres will be suitable for prolonged absorption of domperidone resulted in improved patient compiliance. Further the moringa leaf powder has better mucoadhesive properties and hence can be used as mucoadhesive polymer in various formulations.

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