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DESIGN, CHARACTERIZATION AND IN-VITRO EVALUATION OF SEROTONIN AND ADRENALINE SELECTIVE NEUROTRANSMITTER UPTAKE INHIBITOR DULOXETINE HYDROCHLORIDE: A THIOPENE DERIVATIVE IN TO FLOATING TABLETS

Pharmaceutical

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ABSTRACT

In the present study duloxetine hydrochloride is formulated into gastro retentive tablet dosage form-(floating tablets), duloxetine hydrochloride is a thiopene derivative; it acts as a serotonin and adrenaline selective neurotransmitter uptake inhibitor. Based on the FTIR compatibility between the drug and polymers and review of literature an attempt was made to prepare floating tablets of the drug, where sodium alginate, klucel HXF, Methocel K100 were selected as release retarding agents. Total 14 trials were made, of which sodium alginate and klucel HXF were used till trial T-4, and then only klucel HXF was used till trialT-09 with varying concentrations. Drug release was satisfactory in trial T-09, but floating time, rate of tablet disintegration was not satisfactory, to overcome this Methocel K100 in varying proportions was used to prepare trials from T-10 to T-14. Drug release was 94% in 8 hr. whereas buoyancy time was found to be 12 minutes and floating time was 11hr 45 min. release rate kinetics were also determined by interpreting the release of drug and time into various kinetic models, the order of release was found based on regression coefficient value (R2-value), was found to be 0.989, 0.826, 0.959 and 0.993 and order is as 0.993 KORESMEYER PEPPAS PLOT > 0.989 ZERO ORDER > 0.959 HIGUCHIS PLOT > 0.826 FIRST ORDER..

KEYWORDS

Klucel HXF, Methocel K100, Duloxetine Hydrochloride

INTRODUCTION:

Oral ingestion has long been the most convenient and commonly employed route of drug delivery. The selection of oral route is because of the major advantages offered by intestinal tract, is due to it large surface area, peristaltic movement in GI tract and long residence time gives better residence time for the drug and dosage forms administered through oral route. The maintenance of concentration of drug in plasma within therapeutic index is very critical for effective treatment. These factors as well as factors such as repetitive dosing and unpredictable absorption lead to the concept of oral controlled release drug delivery systems.[2]

The main challenges to oral drug delivery systems are to deliver a drug at therapeutically effective rate to desirable site, modulation of GI transit time and minimization of first pass elimination. The basic rationale of a controlled release drug delivery system is to optimize the biopharmaceutics, pharmacokinetics, and pharmacodynamics properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of disease condition in the shortest possible time by using smallest quantity of drug, administered by most suitable route.[3] The immediate release drug delivery system lacks some features like dose maintenance, controlled release rate and site targeting. An ideal drug delivery system should deliver the drug at a rate dictated by the need of body over a specified period of treatment.[4]

The goal in designing the controlled release drug delivery system is to reduce the frequency of the dosing, reducing the dose and providing uniform drug delivery. Controlled release dosage form is a dosage form that releases one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ. CRDF provide better control of plasma drug levels, less dose frequency, less side effect, increased efficacy and constant delivery.[4]

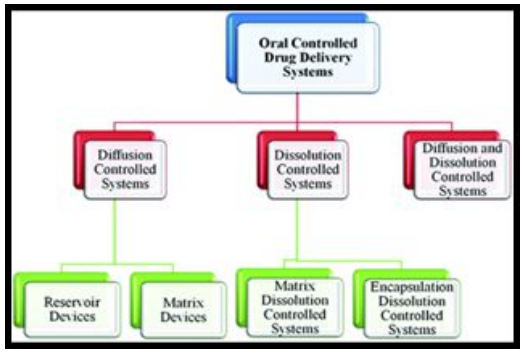

Figure no 01: Classification of oral controlled drug delivery systems

An unpredictable gastric emptying rate that varies from person to person, a brief gastrointestinal transit time (8- 12h), and the existence of an absorption window in the upper small intestine for several drugs have prompted researchers to design a drug delivery system which can stay in the stomach for prolonged and predictable period. One novel approach in this area is "GRDDSs (gastro retentive drug delivery system)". Dosage forms that can be retained in the stomach are called GRDDs.[5]

Gastro intestinal transit times vary widely between individuals, and depend upon the physical properties of the object ingested and the physiological conditions of the gut. This variability may lead to unpredictable bioavailability and times to achieve peak plasma levels[6].

POTENTIAL DRUG CANDIDATES FOR GRDDS:[7]

Table no 01: List of Drug candidates used for gastro retentive drug delivery dosage forms

Acting locally in the stomach	absorbed in the stomach	Poorly soluble at an alkaline pH	Narrow window of absorption	Degrade in the colon
Misoprostol, Antacids	albuterol, amoxicillin.	diazepam, Chlordiazepoxide, verapamil HCl	L-Dopa, para amino benzoic acid, furosemide, riboflavin, ranitidine HCl	Captopril, Ranitidine HCl, Metronidazole etc.

Table no 02: Gastric Emptying Phases[8]

PHASE	TYPES	DESCRIPTION	DURATION (Min)
Phase – I	Basal Phase	Period of no contraction	30 to 60
Phase – II	Pre Burst Phase	Period of intermittent contraction	20 to 40
Phase - III	Burst Phase	Period of regular contraction at the maximal frequency that migrate distally	10 to 20
Phase - IV	Transiting phase	Period of transition between phase III and phase I	0 to 5

Table no 03: description of stomach and small intestine[9]

Section	Length-Mtr	Transit Time-Hr	PH	Microbial Count	Absorbing Surface Area-M	Absorption Path
STOMACH	0.2	VARIABLE	4-Jan	<103	0.1	Passive Diffusion, Aqueous Channel Transport, Active Transport
SMALL INTESTINE	10-Jun	3±1	5-7.5	103-1010	120-200	Passive Diffusion, active transport, aqueous channel transport, facilitated transport, ion-pair transport, pinocytosis and carrier mediated transport

Inter gastric motility pattern:[9]

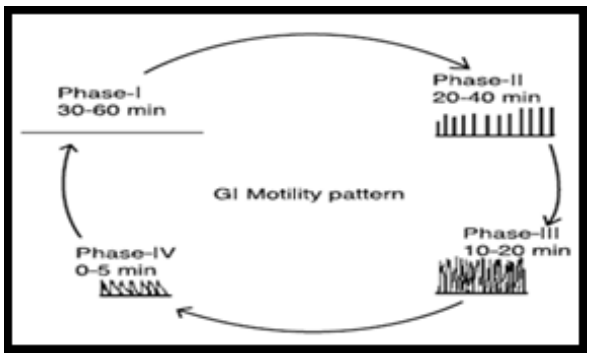

Figure no 02: Intra gastric motility

Phase I is basal phase, which is silent period of 30-60 minutes and characterized by lack of secretory, electrical and contractile activity and there is no contractions.

Phase II is pre-burst phase, which exhibit intermittent action for 20-40 minutes. Some bile secretion started and contractile motions increases frequency. Mucus discharge is started during later part of phase II.

Phase III is burst phase, which is characterized by intense and large regular contractions termed as "house keeper waves". These waves sweep off undigested food by maximizing the pyloric opening and lasts for 10-20 minutes. Thus, these phases enable efficient evacuation of the stomach contents.

Phase IV This is a short transitory period of about 0 to 5 min and the contractions dissipate between the last part of phase III and quiescence of phase I.

The whole MMC cycle is repeated every 2-3 hours.
The motor activity in the fed condition is induced 5-10 min after the ingestion of the meal and persists as long as food remains in the stomach.

The larger the amount of food ingested, the longer the period of fed activity, with usual time spans of 2-6 hrs and more typically 3-4 hrs. Its phasic contractions are similar to those seen during phase II of the MMC.

ABSORPTION WINDOW:

Some drugs are only soluble at a particular pH or they are **absorbed** using a specific mechanism. With such properties those drugs can only be absorbed in **specific segments** of the G.I tract. Those **particulars egments** are named as **"Absorption Windows".**

Many drugs exhibit absorption windows in particular portion of G.I tract which can limit the bioavailability of orally administered compounds and can be a major obstacle to the development of controlled release formulations for such regional specific drugs. Various approaches to increase the residence of drug formulations at or above the absorption window to enhance the bioavailability of such drugs are discussed below.

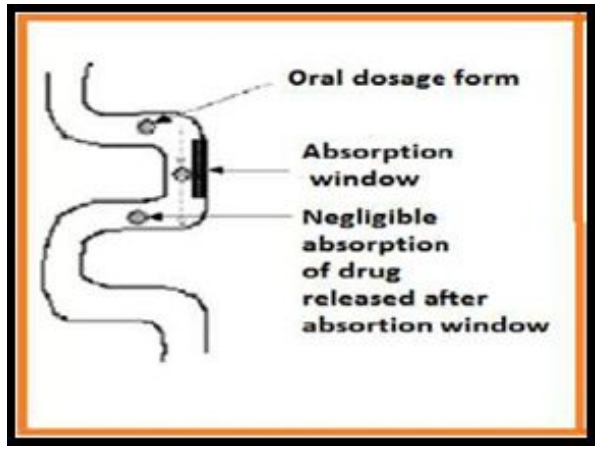

Figure no 03: Drug absorption in case of narrow absorption window

Different approaches presently being explored:

- Modification of intestinal transit time
- Bioadhesive microspheres that have a slow intestinal transit.
- The gastro-retentive dosage system, which is further divided into several approaches like Floating, Swelling, Expanding, etc.

Modification of intestinal transit time

Pharmacological Approach:-

It is fact that some drug can alter GI transit for e.g. pre treatment with Metoclopramide decreases gastric emptying time and increases GI motility, whereas pre treatment with Propenthalein had the opposite effect.

The extent of Metformin absorption (a drug preliminary absorbed from upper intestinal tract) is improved when GI motility is slowed.

Nature's Approach:-

Some dietary component such as fats, certain amino acids and peptides

can slow gastric emptying and intestinal transit.
A lesser known phenomenon is Ileal Brake.
This breaking mechanism appears to be feedback process for the improved digestion of dietary components such as fats.

Bioadhesive microspheres
The idea of bioadhesive began with the clear need to localize a drug at a certain site in the GI tract. Therefore a primary objective of using bioadhesive systemsorally would be achieved by obtaining asubstantial increase in residence time of thedrug for local drug effect and to permit oncedaily dosing.

Gastroretentive drug delivery systems
Gatroretentive dosage forms are designed to be retained in the gastric region for prolonged time and release incorporated drug candidates and thereby enable sustained and prolonged input of the drug to the GIT thus ensuring its optimal bioavailability.

GRDDSs can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site.

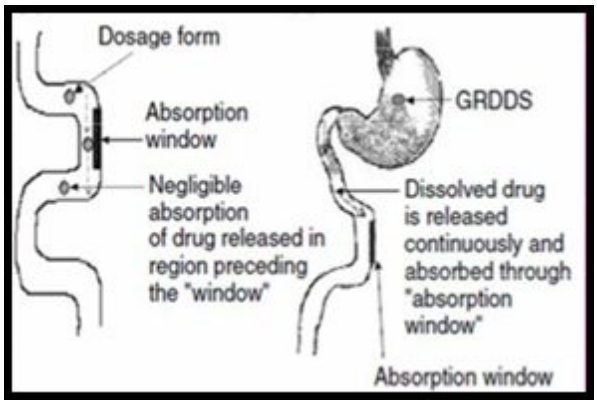

Figure no 04: Drug absorption in GRDDS

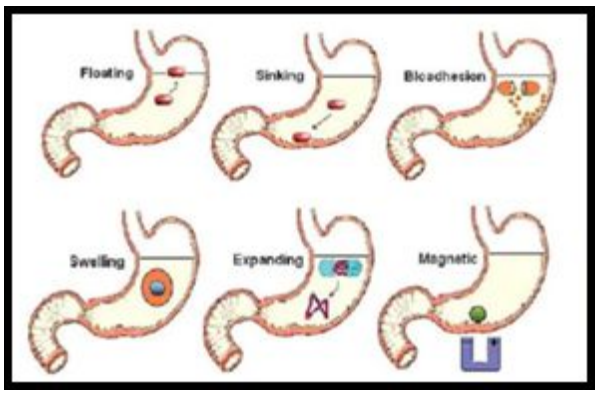

Figure no 05: Types of floating tablets

MATERIALS AND METHODS:[10,11]

Methodology:

Preformulation Studies:
It is one of the significant requirements in expansion of some drug transport system. Preformulation studies are done on the drug, which involved explanation, solubility, pH, and compatibility studies.

Organoleptic Characters:
The organoleptic characters and appearance was noted using vivid terms.

Melting point determination:
The MP of the drug sample was determined by capillary method using melting point apparatus The Reported and observed Melting point is 171-174°c

Determination of solubility:
The solubility of Duloxetine Hcl was determined by totalling surplus amount of drug in the solvent and balanced solubility was determined by taking the supernatant and analyzing it spectro photo metrically with water, 0.1N HCL, Methanol, 6.8pH buffer, chloroform and Alcohol by using the below formula:

%solubility = sample absorbance/ standard absorbance *dilution factor*100

Analytical Method Development of Duloxetine HCL:
Preparation of 0.1 N HCL:
8.5 ml of concentrated HCl was taken and dilute with distilled water up 1000ml.

Determination of λmax of Duloxetine HCL using 0.1 N HCL:

Procedure:
Working standard: 5mg of Duloxetine was taken and dispersed in 100 milli litre of
0.1N HCl gives 50µg/ml concentrated stock solution.

Dilutions:
From the working standard solution 1ml was diluted to 100ml with 0.1N HCL 5µg/ml concentrated solutions.

The similar steps are repeated for 2ml stock solution with 8 ml of HCL and make volume to 10 ml which in turn is 0.2 ml i.e 10µg/ml.

The same is repeated taking 3ml,4ml,5ml,6ml till 8ml with the corresponding concentrations which are 15µmg/ml, 20µg/ml , 25µg/ml, 30µg/ml, 35 µg,ml, 40 µg/ml.

Solutions undergo scanned at 200-400nm wavelength resultant scan spectrum is noted.

The resultant wavelength requiring peak absorbance is known as λmax
Construction of standardisation curve of Duloxetine HCl 0.1N HCl:
Procedure: 5mg of Duloxetine was weigh up and dissolved and then invented to a volume of 100ml with 0.1N HCL 50µg/ml stock solution.

Dilutions:
From the working standard solution 1ml was diluted to 10ml with 0.1NHcl 5 µg/ml concentrated solution.

From dilution 1, take 0.2, 0.4, 0.6, 0.8 and 1 ml and was dilute up to mark in 10ml flask to obtain 2, 4, 6, 8 and 10 µg/ml concentrated solutions. This solutions absorbance was noted at λ_{max}=289µm

Table no 4: Concentration for calibration curve

CONCENTRATION	ABSORBANCE
10µg/ml	0.228
20 µg/ml	0.293
30 µg/ml	0.438
40 µg/ml	0.575
50 µg/ml	0.676

Y=0.014x+0.088
R2= 0.937

Angle of Repose (θ):

It is the maximum angle between the lower surface of a stack of powder and the flat plane.

It is measured using the funnel method. Precisely weighed Microsphere mixture is in use in the funnel. Stature of cone was accustomed in a way the angle of the funnel just touched the topmost of the powder mixture. Microsphere mixture was permitted to flow over the funnel easily on to the lower surface. Diameter of the powder was measured and θ was calculated using the following formula:

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

Where:
p = Angle of repose
h = height
r = radius
The viewpoint of rest has remained used to portray the flow properties. It is characteristic linked to inter particulate resistance or resistance to association amongst particles.

Table no 5: Flow possessions and conforming angles of repose

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

DENSITY:

a) Bulk Density: (BD)

It is the proportion of entire bulk of powder to the bulk size of powder The complete amount of Microspheres in each individual trial are taken carefully and measured using a measuring cylinder.

Firstly the trial 1 is measured then T2, T3, T4…..respectively.

The BD is given:

Bulk density = heaviness of powder / Bulk volume.

$$\mathbf{Pp} = \frac{M}{V_0}$$

M = quantity of the powder
V_0 = unpackaged volume of the powder.

Tapped Density:

Is the proportion of complete bulk of powder to the tapped size of powder. The entire amount of Microspheres in each individual trial are taken carefully and measured using a measuring cylinder. Then the microspheres are tapped first at100times then the vales are notes. Next after 100 taps more 100 taps are done i.e200 and volume of the microspheres is noted. Firstly the Trial 1 is measured then T2, T3, T4…..respectively.

The TD is given by following formula:

Tapped density = Weigh up of powder / Tapped volume

Dt = (M) / (V f).

M = quantity of the powder
V_f = tapped size of the powder.

Determination of Partition Coefficient

Partition coefficient is the fractional concentration of solute in two insoluble or slightly soluble liquids, in two solids, when it is in evenness across the crossing point stuck between them.

100 ml of N- octanol (oily phase) ,100 ml of Distilled H20 (aqueous phase) and taken in a beaker and are mixed properly. Then to it 100 mg of Duloxetine HCl (drug) is added and mixed thoroughly.

Then the mixture is use in a separating funnel and shaken vigorously to separate the oily and aqueous phase .shake well for about 15-20 minutes till the two phases gets separated.

Then slowly take the oily an aqueous phase in different beakers or flasks and let the drug get separated using Filter paper.

Now that the phases are separated, take the absorbance using UV spectrophotometer.

Partition Coefficient is given by the following formula:

$P_{o/w}$ = Organic phase/ Aqueous phase x 100

Preparation of gastro retentive floating tablets

- Floating tablets of Duloxetine HCl was prepared by direct compression technique using variable concentrations of Klucel HXF, Methocel K100, and Klucel HF with gas generating agents such as sodium bicarbonate and citric acid.
- Weigh all the ingredients accurately and transfer them carefully in a motor.
- Triturate the above transferred ingredients thoroughly.
- Check for

1) Bulk density
2) Tapped density
3) Angle of repose
4) Compressibility index
5) Particle size distribution

- Finally subject the prepared tablet powder to compression.
- Each tablet contained 20 mg of duloxetine hydrochloride.
- Composition of all the formulation is shown in below table.

Formulation of duloxetine hydrochloride floating tablets:

Table no 6: Ingredients used in formulation of GRDDS tablets from trial T-01 to T-09

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Duloxetine HCl	40	40	40	40	40	40	40	40	40
Klucel HXF	15	30	45	60	75	90	105	120	135
Sodium Alginate	25	50	100	125	-	-	-	-	-
Lactose	100	175	200	225	250	300	350	350	350
starch	5	5	5	10	10	10	10	10	10
MCC	125	75	100	100	100	100	51	101	151
Citric acid	20	20	15	15	15	18	18	22	22
Sodium Bicarbonate	20	20	20	15	15	18	18	22	22
Tartaric Acid	10	20	20	-	-	-	-	-	-
Magnesium Stearate	5	5	5	6	5	5	6	6	6
Talc	5	5	5	6	5	5	6	6	6
total weight	370	445	555	602	515	586	604	677	742

Table no 7: Ingredients used formulation trials T-10 to T-14

INGREDIENTS	F10	F11	F12	F13	F14
Duloxetine HCl	40	40	40	40	40
Methocel K100	50	75	100	125	150
Lactose	100	100	100	100	100
Starch	10	10	10	10	40
MCC	25	50	100	150	200
Citric acid	5	5	8	10	20
Sodium Bicarbonate	5	5	8	10	20

Magnesium Stearate	5	5	5	5	6
Talc	5	5	5	5	6
weight of the tablet	245	295	376	455	582

EVALUATION PARAMETERS:
Evaluation of powder blend

Angle of repose
The angle of repose of powder blend was determined by the funnel method. The accurately weighed powder blend was taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured n angle of repose was calculated using the following equation.

$\tan\theta = h/r$
Where, h and r are the height and radius of the powder cone.

Bulk density
About 10 gm of powder was weighed and transferred in a 100ml measuring cylinder. The amount of volume occupied was noted. The bulk density was calculated by the using the below equation
Bulk Density=mass/volume

Tapped density (TD)
Transfer accurately weighed 10 gm of powder in a 100 ml measuring cylinder. Place the cylinder in a tapped density tester. Tapping is done mechanically and it is continued until no further change in volume was observed. It is calculated by the following equation.

Tapped Density = Mass of the powder / Tapped volume of the powder

Compressibility Index
It is calculated by using the following equation,

$CI(\%) = [(TD-BD) \times 100] / TD$

Hausner's ratio
It is calculated by dividing the tapped density (TD)by bulk density (BD).

Evaluation of tablets
Weight variation test
To study weight variation, twenty tablets of the formulation were weighed using a electronic balance and the test was performed according to the official method as mentioned in standard pharmacopoeia. Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation.

Test for Hardness
It is done to know whether the tablet can withstand mechanical shocks while transportation and handling. This test is carried out using Monsanto hardness tester. It is expressed in kg/cm^2.

Thickness
Thickness of the tablet is calculated by using Vernier calipers.

Friability test
It is determined using Roche Friabilator. It is expressed in percentage (%).20 tablets were weighed (X). The friabilator was run up to 100 revolutions at 25 rpm for 4 minutes. The tablets were weighed again (X0).

$F = [1 - X / X0] \times 100$

In vitro buoyancy studies
The in vitro buoyancy is represented by floating time and floating lag time. The tablet was placed in a USP type 2 dissolution apparatus containing 900 ml of 0.1 N HCl and the paddle is rotated at a speed of 50 rpm. The time between introduction of dosage form and its buoyancy in 0.1N HCl and the time taken by the system to remain buoyant was noted. The time taken for the dosage form to emerge on surface of medium is called Floating Lag time (FLT) or Buoyancy Lag Time (BLT). Total time by which the dosage form remain buoyant is called Floating time (FT).

Determination of Drug Content
How much amount of drug is present in formulation is known by calculating percentage Drug Content. The result should be within the limits given by the standard monographs. By using HPLC, HPTLC methods, near Infrared spectroscopy (NIRS), Micro-titrimetric methods, etc the drug content can be determined.

Swelling studies
It is carried out in dissolution apparatus.
Swelling index:- the swelling dosage form is immersed into medium at 370C in dissolution apparatus. Dosage form is taken out at equalr intervals and any dimensional changes are observed and noted in relation to increase in diameter with time or tablet thickness.

Water uptake:- the dosage form is taken out at equal regular intervals and the change in weight with respect to time is measured. It is also called as weight gain.

Water Uptake = $WU = [(W_t - W_0) \times 100] / W_0$
Where, W_t = Weight of dosage form at time t
W_0 = Initial weight of dosage form

In Vitro Dissolution Studies
The release rate of Duloxetine Hydrochloride from floating tablets was determined using The United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method).

The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 8 hours, and the samples were replaced with fresh dissolution medium. The samples diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 289 nm using a UV-Vis spectrophotometer.

Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

Stability studies:
According to ICH guidelines the prepared tablet dosage forms are kept for stability studies at accelerated conditions and room temperature.

Results and Discussion:
Preformulation parameters:
Duloxetine characterization:

Table no 8: physical characterization of API

S.no	API Characterization	Results
1	Physical Appearance	White powder
2	Melting point	159oC
3	Solubility	Methanol, water
4	Bulk density	0.27gm/ml
5	Tapped Density	0.73gm/ml
6	Carr's index	19.32
7	Hausner's Ratio	1.83

Analytical method, calibration curve of duloxetine hydrochloride

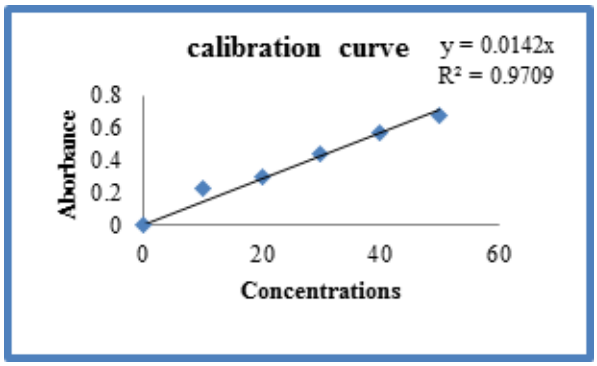

Figure no 06: Calibration curve of duloxetine hydrochloride in 0.1N. HCL

FTIR COMPATIBILITY STUDIES:

In the present study, API Duloxetine hydrochloride and polymers were studied for compatibility studies using FTIR Technique for the determination of any interference between the drug and polymers. FTIR spectra are given in following figures.

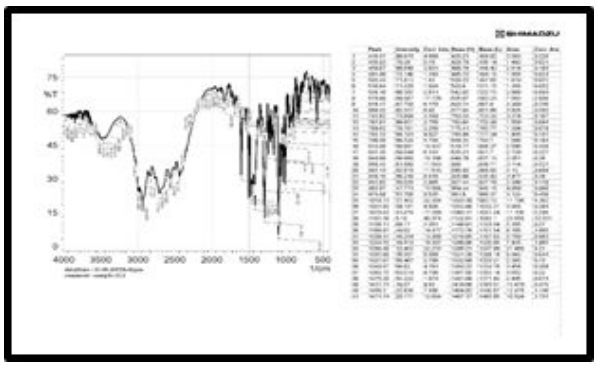

Figure no 07: FTIR spectra of duloxetine hydrochloride

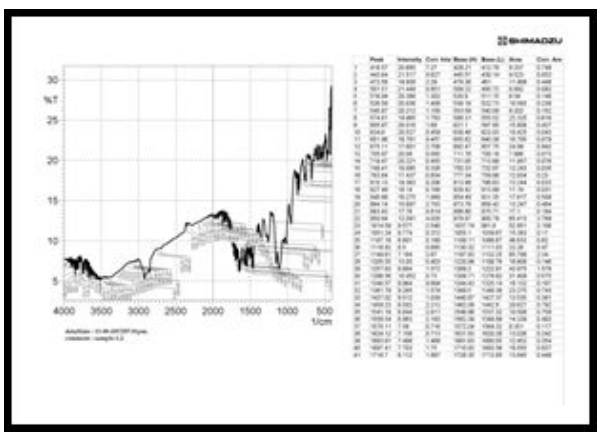

Figure no 08: FTIR spectra of KLUCEL HXF

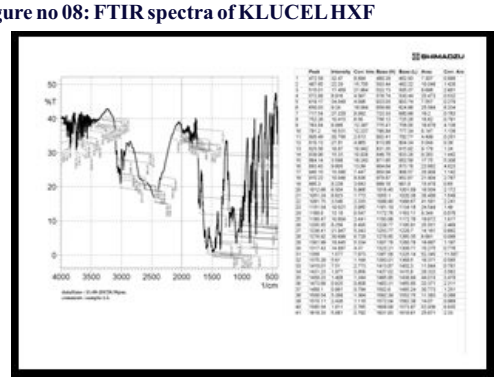

Figure no 09: FTIR spectra of Methocel K100M

IN-VIRTO EVALUATION:

Characteristic properties of blend:

Table no 9: Micrometrics Properties of final blend of trial-01 to trial T-09

Trial	Carr's index	Tan Ø	Hausner's ratio	Bulk Density
F1	6.25	25.25	1.08	0.25
F2	8.73	26.32	1.04	0.65
F3	6.97	23.82	1.03	0.46
F4	9.75	29.5	1.02	0.65
F5	7.67	27.2	1.15	0.87
F6	8.65	28.73	1.12	0.87
F7	10.47	29.73	1.02	0.65
F8	9.73	22.17	1.18	0.77
F9	8.49	27.62	1.15	0.87

Table no 10: Micrometrics Properties of final blend of trial-10 to trial T-14

Trial	Carr's index	Tan Ø	Hausner's ratio	Bulk Density
F10	8.21	22.64	1.03	0.21
F11	7.93	24.81	1.08	0.36
F12	6.81	21.71	1.06	0.63
F13	7.93	23.81	1.07	0.26
F14	7.27	26.19	1.83	0.71

Table no 11: In-vitro evaluation of tablets from triaT-01 to T-05

Parameters	F1	F2	F3	F4	F5
Weight Variation	367-374	441-446	552-556	598-604	513-518
Friability	0.13	0.83	0.13	82	0.37
Hardness	7.2-8.4	7.5-9.4	7.3-10.2	8.2-10.6	9.3-11.8
Thickness	14-16	14-17	14-18	13-17	13-16
Content Uniformity	99.25	100.3	101.8	98.2	98.2

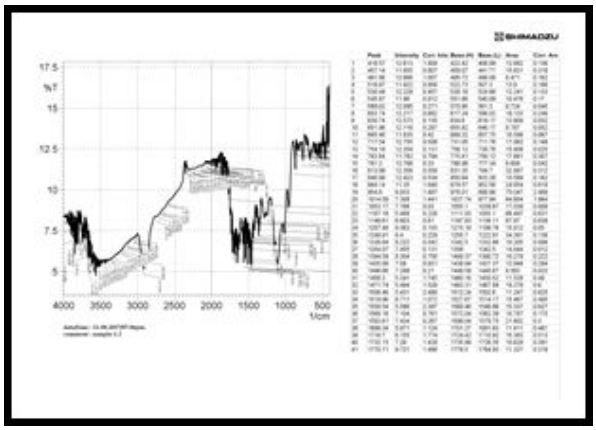

Figure no 10: FTIR spectra of optimized trial T-14

Table no 12: In-vitro evaluation of tablets from triaT-06 to T-09

Parameters	F6	F7	F8	F9
Weight Variation	584-590	602-608	674-679	740-746
Friability	0.27	0.75	0.74	0.43
Hardness	10.4-13.1	10.5-14.3	8.4-10.4	12.4-14.5
Thickness	13-17	12-16	12-17	12-14
Content Uniformity	99.37	99.28	101.38	100.38

Table no 13: In-vitro evaluation of tablets from triaT-10 to T-14

Parameters	F10	F11	F12	F13	F14
Weight Variation	240-242	290-296	372-378	452-458	578-584
Friability	0.23	0.34	0.21	0.21	0.46
Hardness	12.2-14.3	11.2-14.6	12.4-16.4	12.4-14.6	12.6-12.4

Thickness	14-16	14-17	14-18	13-17	13-16
Content Uniformity	99.25	100.34	101.84	98.23	98.23

In-vitro Buoyancy and floating time:

Table no 14: Lag phase and floating time of trials T-01 to T-09

Formulation	Buoyancy Lag Time-min	Floating Time
F1	3'25	>8hr
F2	8'45	8.34 hr
F3	6'16	8.24hr
F4	10'45	9.25hr
F5	15'20	10.34hr
F6	16'40	10.22hr
F7	14'40	10.45hr
F8	20'40	11.42hr
F9	18'20	11.22hr

Table no 15: Lag phase and floating time of trials T-10 to T-14

Formulation	Buoyancy Lag Time-min	Floating Time
F10	6'24	10.25hr
F11	10'22	10.14hr
F12	15'22	11.24hr
F13	18'22	10.24hr
F14	12'18	11.45hr

In-Vitro Drug Release Studies:

Table no 16: Drug release data form trial T-1 to T04

Time	F-1	F-2	F-3	F-4
0	0	0	0	0
30	18.34	16.38	14.28	18.39
60	22.82	19.37	18.18	26.55
120	36.12	29.81	24.19	37.39
180	45.18	49.34	34.19	49.28
240	63.28	62.81	55.38	55.29
300	73.18	74.28	68.29	73.28
360	84.28	81.84	75.93	89.82
420	94.46	99.12	89.47	100.23
480	99.28	101.31	99.21	101.37
540	97.37	97.38	97.38	95.28
600	95.27	96.82	98.39	76.28

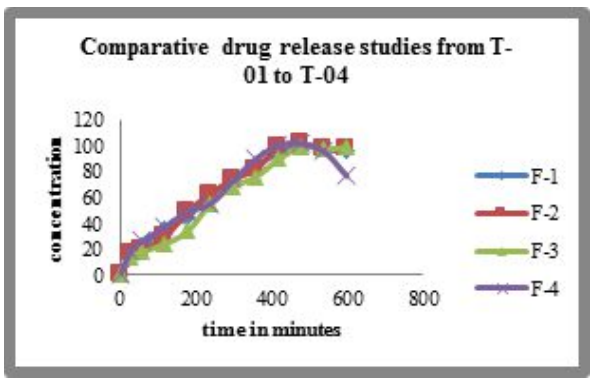

Figure no 11: Graphical representation of drug release form trial T-01 to T-04

Table no 17: Drug release from trial T-5 to T-9

TIME	F-5	F-6	F-7	F-8	F-9
0	0	0	0	0	0
30	15.23	8.38	9.29	12.19	15.32
60	17.39	13.18	15.29	25.38	21.83
120	28.82	18.29	27.28	29.39	37.19
180	39.27	28.83	37.18	45.29	49.29
240	58.28	38.28	45.81	63.92	61.91
300	68.29	66.83	59.17	73.28	76.18
360	77.27	78.29	84.28	89.82	89.82
420	89.76	86.27	94.28	100.23	95.19
480	99.72	99.28	96.28	101.37	98.83
540	96.27	97.38	101.01	95.28	100.1
600	98.72	96.82	95.91	76.28	99.87

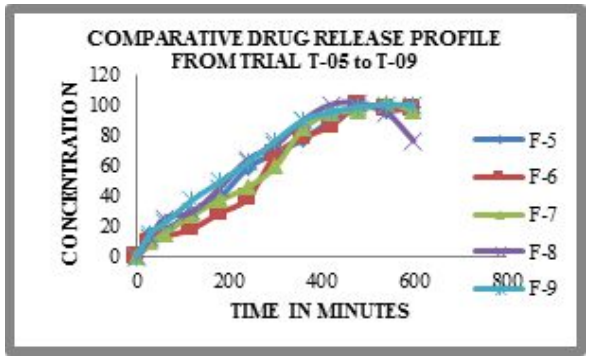

Figure no 12: Comparative drug release form T-05 to T-09

Table no 18: Drug release data from trial T-10 to T-14

TIME	F-10	F-11	F-12	F-13	F-14
0	0	0	0	0	0
30	25.19	28.19	21.93	18.38	14.93
60	29.19	36.38	38.27	21.39	25.28
120	46.87	48.73	47.81	31.85	36.48
180	54.78	55.92	55.29	42.18	48.19
240	75.98	68.81	64.82	58.39	59.37
300	89.65	76.82	74.28	78.18	67.38
360	98.67	81.83	81.83	85.75	73.19
420	96.84	89.48	99.19	98.17	85.53
480	93.72	98.67	101.3	99.93	94.47
540	91.37	101.8	99.18	101.4	99.58
600	96.28	98.38	97.73	95.28	100.3

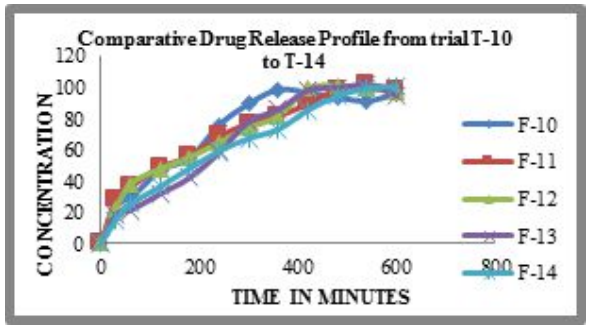

Figure no 13: Drug release profile from trial T-10 to T-14

In-vitro evaluation of optimized trial T-14

Table no 19: Physical Properties of final blend of optimized trial T-14:

Parameter	F-14
0.294	0.497
TBD, mg/cc	0.638
Angle of repose	18.83
Compressibility, %*	23.93
Drug content, %**	100.2
Uniformity of weight, mg*	584

Table no 20: Drug release from optimized trial T-14

TIME IN MIN	F-14
0	0
30	15.45
60	21.93
120	29.18

180	39.18
240	45.47
300	57.84
360	68.62
420	78.29
480	89.28
540	95.29
600	101.84

Determination of release rate kinetics:

Table no 21: Release rate kinetics of optimized trial T-14

ZERO ORDER		FIRST ORDER		HIGUCHIS		KORESMEYER PEPPAS PLOT	
Time In Min	% Drug Undissolved	Time In Min	Log 100-Q	Sq. Time	Mean % Drug Dissolved	Log Time	Log Cumulative % Drug Dissolved
0	100	0	2	0	0	0	0
30	84.55	30	1.93	5.48	15.45	1.48	1.19
60	78.07	60	1.89	7.75	21.93	1.78	1.34
120	70.82	120	1.85	10.95	29.18	2.08	1.47
180	60.82	180	1.78	13.42	39.18	2.26	1.59
240	54.53	240	1.74	15.49	45.47	2.38	1.66
300	42.16	300	1.62	17.32	57.84	2.48	1.76
360	31.38	360	1.50	18.97	68.62	2.56	1.84
420	21.71	420	1.34	20.49	78.29	2.62	1.89
480	10.72	480	1.03	21.91	89.28	2.68	1.95
540	4.71	540	0.67	23.24	95.29	2.73	1.98
600	-1.84	600	0	24.49	101.84	2.78	2.01

Graphical Representation of release rate kinetics:

Zero Order:

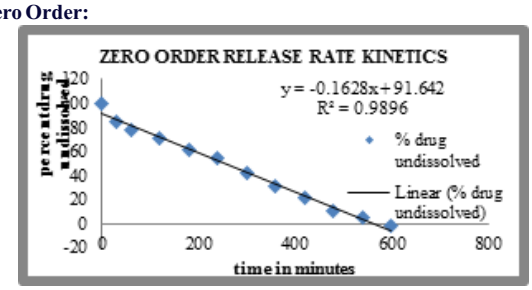

Figure no 15: Zero order release rate kinetics from T-14

First Order:

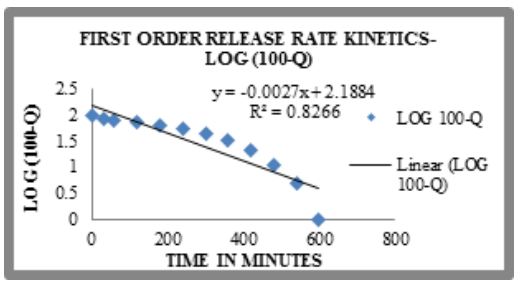

Figure no 16: First order release rate kinetics from T-14

HIGUCHIS MODEL:

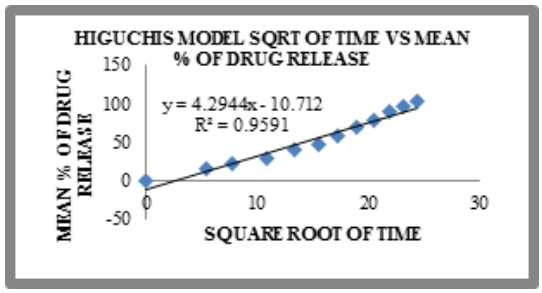

Figure no 17: Higuchis Model of release rate kinetics from T-14

Koresmeyer Peppas Model:

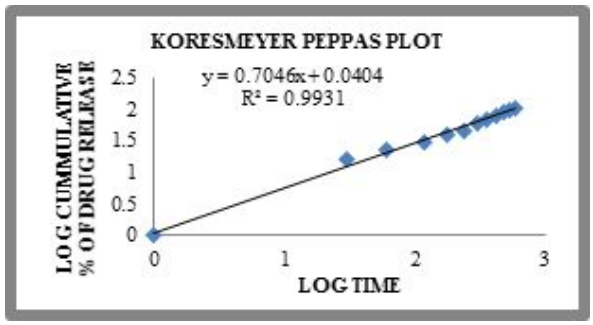

Figure no 18: Release rate kinetics of Koresmeyer Peppas Model from T-14 Percent of Water Uptake and Axial Swelling Studies:

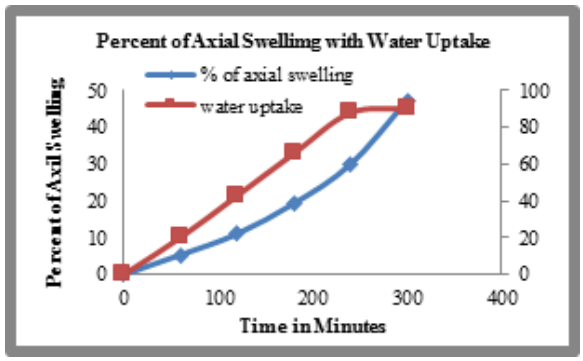

Figure no: Water Uptake and Percent of Axial Swelling from T-14

Polymer erosion studies:

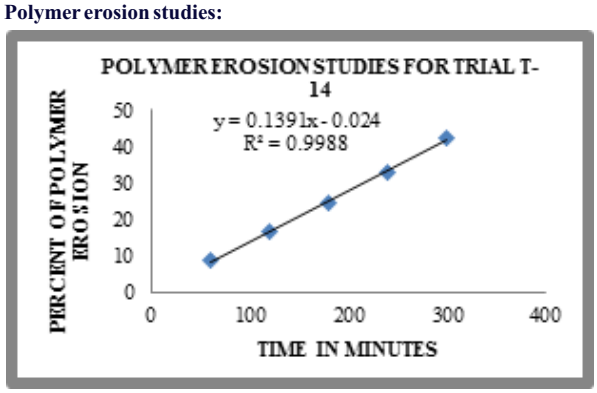

Figure no 19: Rate of polymer erosion of tablet T-14

Discussion:

In the explanation as discussion on the results obtained in the present research work, first am pleased to inform regarding the compatibility studies performed, between API duloxetine hydrochloride and polymers used klucel and Methocel K100, were run for FTIR and the spectra of FTIR gave the peaks which are independent and are not interfering much with each other.

Based on the compatibility studies and review of literature of API and polymers used, initiation of formulation trials was taken place from T-01 to T-14.

In initial trials form T-01 to T-04; Floating tablets were prepared using KLUCEL and SODIUM ALGINATE along with other common polymers in preparation of floating tablets.

Use of sodium alginate was no much advantageous, as the lag phase and floating time was not satisfying.

As the lag phase time taken from tree minutes for T-1 to 10 minutes for T-4 and where as floating time was minimal in all trial, the reason behind might due to present of sodium alginate, and less percent of polymer KLUCEL.

From trials T-05 to T-09, proportional increase of hydrophilic polymer KLUCEL was taken, in same ratio lag phase and floating time were attaining satisfying timings.

Physical characterization blend of all trials for T-01 to T-09 were showing good results and are within the limits according to standard specification.

In-vitro release studies were satisfying from trial T-09, details of drug release can be interpreted from table no 17 and explained graphically in figure no 12.

A further attempt for formulation of floating tablets of duloxetine hydrochloride was carried out by taking Methocel K 100 from trials T-10 to T-14 in increasing proportionate.

Trial T-14, was optimized based on drug release studies and was taken for one month accelerated stability studies and the drug release was similar rate as with that of the trial T-14 kept at room temperature.

The release of drug was taken for determination of release rate kinetics by interpreting the data in different kinetic models. Base on the regression coefficient value (R2-value), was found to be 0.989, 0.826, 0.959 and 0.993 and order is as 0.993 KORESMEYER PEPPAS PLOT > 0.989 ZERO ORDER > 0.959 HIGUCHIS PLOT > 0.826 FIRST ORDER.

Base on R2 value release rate of duloxetine hydrochloride in-house prepared floating tablets was found to be following Koresmeyer Peppas Plot with R2 value 0.993.

As drug release will depend on polymer swelling, water uptake and rate of polymer erosion for hydrophilic polymers, rate of polymer axial swelling with water uptake studies and polymer erosion studies were also performed, and the results were found to swelling of Methocel K100 was found to be with the amount of water uptake and polymer erosion was found to be constant with respective to time.

Based on the satisfactory results obtained, the prepared and optimized formulation trial T-14 with Methocel K100, further it can take for further studies.

Acknowledgement:

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