Original Research Paper

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Pharmaceutical

FORMULATION AND IN-VITRO EVALUATION OF CONTROLLED RELEASE MICROSPHERES OF DULOXETINE HYDROCHLORIDE

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ABSTRACT Duloxetine Hydrochloride is a FDA approved is Serotonin and Nor-epinephrine reuptake inhibitor (SNRI) Anti-depressant drug, which is sold under the name Cymbalta. It shows good bioavailability, averaging up to 50% upon oral administration and its lambda max was found to be 289nm. Floating microspheres after administration orally, resist in stomach for long period of time to increase the bioavailability of the drugs which has the maximum absorption site from proximal part of the small and large intestine. After oral administration of Duloxetine Hcl would be stay in the stomach and issue the drug in a sustained manner, so that the drug could be released unceasingly to its site of absorption in the upper GIT. This method of administration would be finest achieving the effect of the drug. Based on this, an effort was made to design Controlled release Microspheres of Duloxetine hydrochloride using different proportions of polymers and combinations.

In the present effort, an effort has made to develop controlled release Microspheres of Duloxetine hydrochloride by selecting Sodium Alginate and Methocel E50 as checking polymers. The polymers are used in different ratios of groupings. All the formulations were prepared by Solvent Evaporation method. The preparation of all the formulations showed respectable flow properties such as angle of repose, bulk density, tapped density. The prepared Microspheres show good post formulation parameters such as content uniformity, percentage yield, dissolution studies, stability studies and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations T6 and T8 formulation showed maximum % drug release, but the ideal formulation was found to be T8 for showing best drug release i.e., 100% in 10 hours. Hence it is considered as optimized formulation with the least possible concentration of polymers. It was observed that the combination ratio of Sodium Alginate 400mg and Methocel E 50 20mg has distinct effect on in vitro drug release profiles when compared to all the other combinations of polymers.

KEYWORDS : Duloxetine Hydrochloride, Sodium Alginate, Methocel E 50, Controlled release Microspheres.

INTRODUCTION:

Route of Administration of drug from oral cavity is the most suitable and broadly used route for drug administration. It is great patient suitability, mainly due to comfort of administration. Over the ages, oral dosage forms has become ever more refined with main role being played by organized issue drug supply systems i.e Controlled systems to release drug at fixed rate.[1]

Drug delivery skills are progressive enough to design any dosage form that can deliver drugs at a persistent amount for lengthy period of time extending from many days to several years. However most oral controlled issue dosage forms transport drugs for 12hours. Oral delivery for 24 hrs is likely for some drugs, such are immersed well through Gastro Intestinal Tract (GIT). So, the actual issue in the growth of oral release controlled dosage forms is to cover the time for absorption of drug to intestine. [1]

As instance, Oral dose systems might have to halt in the stomach or anywhere in the higher small intestine till the whole drug is out for anticipated period of time. Scheming stages that mark upper small intestine is rather struggle, since they would have to be adhesive type arrangements that selectively stick to to jejunum, ileum surface. Yet, it is difficult to place oral dosage forms at certain sites in the small intestine. For this cause research hard work have been concentrated on platform to spread Gastric Retention Time (GRT)[1]

MICROSPHERES:

Microspheres are small, impenetrable, free rolling round particles containing a polymer matrix and drug and size about 50 nm to 2 mm. Nanospheres is the term often related to the lesser spheres (sized 10 to 500 nm) to differentiate them from bigger microspheres. Ideally they are totally spherical and equal in size. Microspheres are prepared from polymer, wax and protecting materials that is recyclable artificial polymers and adapted natural produces.

Microspheres are made in hard and deep form. Hollow microspheres are cast-off in addition to low the mass of a material. Solid recyclable microspheres combining a drug dispersed over unit matrix have the latent for control release of the drug.

They acknowledged much care not only for extended release but also for the pointing Neoplastic drugs to tumour.Well-made control drug distribution scheme can fix some of the glitches of conventional remedy and expand the therapeutic competence a drug. Many methods are used for carrying a therapeutic material to the target site in a continuous controlled release manner.

Example one method is using spheres as transporters for drugs. It is the consistent means to deliver the drug to the aim site with specificity, if altered, and to maintain the desired focus at the point of interest without unfortunate effect. Microspheres expected much care not only for extended issue, but also for aiming to tumour. In the future by uniting of the various other approaches, microspheres will find the chief place.

TYPES OF POLYMER	EXAMPLES
1.NATURAL POLYMER: Proteins Carbohydrates	Albumin, Gelatin , Collagen Starch, Agarose, Chitosan
2.MODIFIED NATURAL POLYMERS: Chemically modified Carbohydrates	Poly(acryl) starch, poly (acryl) dextran
3. SYNTHETIC POLYMERS Biodegradable Non-biodegradable	Lactides Glycolides Polyanhydrides Acrolein ,epoxy polymers

in original drug delivery, mainly in unhealthy cell categorization, diagnostics, genetic materials, harmless targeted and actual in vivo supply and enhancements as miniature forms of unwell tissues in the body.[2]

IDEAL CHARACTERISTICS OF MICROSPHERE CARRIERS:[3]

1. Should prolong the duration of action.
2. Capability to aim at specific site.
3. Measured issue of drug.
4. Enhanced therapeutic efficiency
5. Drug protection
6. Poly-valency
7. Lowered toxicity
8. Stability
9. Bio-restorability and biocompatibility
10. Water solubility/ Dispersability.

POLYMERS FOR MICROSPHERES[3]:

CATEGORIZED IN TWO TYPES:

Microspheres used usually made up of polymer. They are categorized into two types:

1. Natural polymers
2. Synthetic Polymers

Natural polymer's found from diverse sources like carbohydrates proteins and chemically altered Carbohydrates.
Carbohydrates: Agarose, Starch, Gelatine

Synthetic polymers are allocated into two types.
a. Recyclable polymers:
E.g. co-polymers of Glycolides,Lactides

b. Non-Recyclable polymers:
E.g. Glycidyl methacrylate, Epoxy polymers.

Chemically modified:
Poly dextran and starch.

Table no 01: Types of Polymers used in preparation of Microspheres[4]

TYPES OF POLYMER:

1.Natural Polymer:
Proteins
CarbohydratesEXAMPLES
Albumin, Gelatin , Collagen
Starch , Agarose , Chitosan

2.Modified Natural Polymers:
Chemically modified
CarbohydratesPoly(acryl) starch, poly (acryl) dextran

3. Synthetic Polymers:
Biodegradable
Non-biodegradableLactides Glycolides
Polyanhydrides
Acrolein ,epoxy polymers

TYPES OF MICROSPHERES:

Bioadhesive Microspheres:[4]
This type of microspheres show a long lasting stay time at the location of use and causes close connection with the absorption site and produce better healing action.

Applications:
Buccal, oral, ocular, nasal Colon drug delivery Nasal – Gentamicin Insulin [5],
GI – Glipizide[6]
Colonic - Insulin [7]
Ocular - Methyl prednisolone[8]

2 Magnetic Microspheres: [9]
Magnetic microspheres are super molecular units that are minor sufficient to flow through passageways without creating embolic blocking (<4μm) but are suitably at risk (ferromagnetic) to be taken in micro vessels and pulled into the neighbouring matters by magnetic field of 0.5-0.8 tesla.

Applications:
DNA analysis, Cell separation, protein decontamination and directing drugs to tumour sites (Doxorubicin)[10]

3. Floating Microspheres:[11,12]
Floating microspheres are low-density structures that have enough flexibility to drift over gastric contents and stay in stomach for extended state without disturbing gastric emptying rate. The drug is releases slowly at the anticipated rate.

Applications:
Drugs like Antiviral, Antifungal and Antibiotic agents, NSAIDS, Prednisolone,
Lansoprazole[13,14]

4. Radioactive Microspheres:
They deliver high radioactivity dose to the directed areas without breaking the normal neighbouring tissue. They are inserted to the arteries which lead to Tumour of notice. Example: α emitters, β emitters ,& γ emitters.[15]

Applications:
In Diagnosis - Diagnostic radio embolization: (MAA)[16], Thrombosis : 99mTc-sulfur colloidal[17], Therapeutics – Radio embolization of liver and spleen tumours , Local radiotherapy[18]

5 .Polymeric Microspheres :[19]
Recyclable polymeric microspheres are which comprise of biodegradable polymers that extends the residence time when derives in interaction to mucous sheath due to it is high grade of swelling nature with aqueous medium , which result in gel formation.

The degree of drug discharge is measured by attentiveness of polymer and the relief pattern in a continued manner. Non-natural polymeric microspheres are made of artificial polymers and used as substance (bulking) agent, fillers, vehicles etc.

Applications[20:]
Hepatitis, Influenza, Pertussis, Diptheria toxoid,Oral drug delivery of simply ruined drugs: Gene therapy, insulin delivery,Issue to proteins, hormones and peptides etc.

TARGETING OF MICROSPHERES:[21]

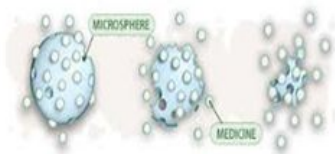
1. Passive Targeting
2. Active targeting
3. Targeting using magnetic microspheres
4. Intracellular targeting

DRUG RELEASE PROFILE OF MICROSPHERES:[22]

Drug release profile commencing microspheres hinge on appearance of the polymer used in the making and the active drug.

Drugs could be free over microspheres by any of the three methods:

1. Osmotically burst mechanism
2. Pore dispersal mechanism
3. Erosion of the polymer.



Close-up of a microsphere dissolving, gradually releasing medicine over time.

Figure No. 01: Drug Release Profile of Microspheres

1.Osmotically focused burst mechanism:
Water spreads into the central over degradable / non-biodegradable covering, making enough pressure that breaks the membrane.

2.Pore diffusion method :
Penetrating water front remain to diffuse in the way of the core. The detached drug/protein softens creating a water filled aperture network and spreads out in precise manner.

3.Erosion of polymer:
Initiates with variations in the small structure of carrier as water enters within it prominent to plasticization of matrix, which leads to breaking of hydrolytic bonds.

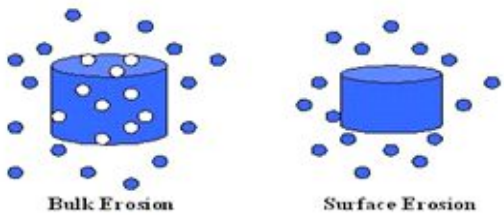


Figure No.02: Erosion of Polymers

Drug Loading And Drug Kinetics Of Microsphers:[23]

Active components are filled over the microspheres mainly by two approaches, i.e. during formation of microspheres and after the formation by keeping warm with the drug/protein.

The active ingredient can be full by physical set-up, chemical association and apparent (surface) adsorption. Entrapment is based on the inner nature to the making of drug /polymer.

Maximum loading can be attained by including the drug during at the time of preparation but it may get affected by other process variables such as method of preparation, additives in the temperature of polymer formation, agitation etc.

Active constituent release is an important concern in instance of microspheres. The issue outline from the microspheres centred on the nature of polymer used in the making as well as of the active drug. Discharge of drug from microspheres is fractional by structure of the transporter and the possessions of the polymer. Drug issue from the Non-recyclable type of polymers can be assumed by seeing the Geometry.

Geometry of the carrier directs overall relief outline the drug. In command to study the precise mechanism of drug from microspheres, dose issue data to Zero and First order, Higuchi equation, and Hixson and Peppa's methods.

Choosing the most suitable model was certain on the results obtained of t test. Zero-order kinetic defines the schemes in which the drug issue rate is free of its concentration. First order kinetic labels are in which the drug issue rate is Attention dependent. Higuchi define the issue of drug from an unsolvable matrix as a root of the time-based process on the base of Fickian diffusion. The Hixson Crowell root law labels drug relief from schemes in which alteration in the surface Part and diameter of particles. Peppas labels when issue of 2 or more than two or the kinetics is not properly known for drug .

$R=k0t$
$\text{Log UR}=k1t2.303$
$R = k2\,t\,½(UR)$
$1/3=k3t\ \text{Log R} = \log k4 + n \log t$
Where R and UR are the issued and not %, at time t. K_0, K_1, K_2, K_3 and K_4 are discharge rate constants all orders and educational methods.

METHODS FOR PREPARATION OF MICROSPHERES:
SOLVENT EVAPORATION METHOD

A) Single emulsion technique:

Mini particulate transporters of natural polymers that of a carbohydrate and protein made. Natural polymers are interfered in liquid medium next spreading cross in the oily medium. Instant step of research, linking of distributed globule is approved. The cross interacting is reached by following that is also by heat or by means of substances i.e Glutaraldehyde and Formaldehyde etc.

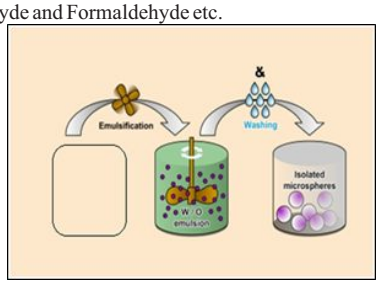


Figure no.03: Single Emulsion technique

b).Double emulsion technique

In this the improvement of the numerous emulsion or double emulsion of w/o/w. Finest suited to water solvable drugs vaccines, proteins and peptides. This way is by both the types naturally obtained as well as simulated polymers. The liquified protein solution is spread in a lipophilic organic non-stop phase .This protein solution may comprise the active ingredients.Continuous phase is usually finally summarizes of the protein controlled in spread.

POLYMERIZATION:

Polymerisation techniques conservatively hand down for the making of the microspheres, are mainly of 2 types

1. Normal polymerisation
2. Interfacial polymerisation

a) Normal polymerization:

Normal polymerisation is done using unpackaged, suspension, emulsion precipitation micellar polymerisation procedures. In unpackaged polymerisation, a chemical entity/ mixture along with the initiator is heated to start polymerization. Polymer obtained is moulded as microspheres. Drug filling is done during the process. Suspension polymerization also called as bead / pearl polymerization. Droplets may contain an initiator. Emulsion varies from suspension due to the occurrence inventor in the aqueous phase, which binds to the surface of micelles. Bulk method has an advantage of creating pure polymers.

b)Interfacial polymerization :

Feedback of numerous monomers at the border among the two immiscible liquid phases to form a layer of polymer that basically encloses the spread phase. In this method two countering monomers are involved, single of which is softened in the Constant phase while the other being spread in the continuous phase.

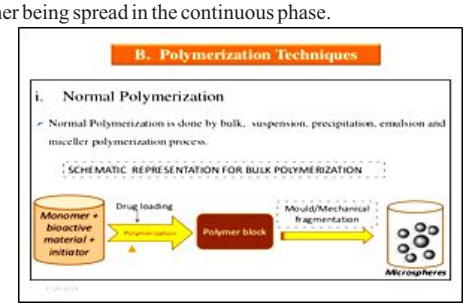


Figure no: 04-Polymerization Techniques

COACERVATION/PHASE SEPARATION:

This is used for preparation of the reservoir systems. It is used to cover water soluble drugs such as peptides, if lacking affinity towards water e.g. steroids. In this process the polymer is mostly liquefied in appropriate solvent and then drug is spread by preparing its aqueous solution, hydrophobic polymer solution itself. Point separation is then achieved by changing the conditions of the solution by the Adding of salt, solvent, incompatible polymer, and change in PH.

Trial/Ing.	Na. Alg	Water	Drug	$CaCl_2$5%	Methocel E 50
T-1	150	20	20	5	--
T-2	200	20	20	5	--
T-3	250	20	20	5	--
T-4	300	20	20	5	--
T-5	350	20	20	5	--
T-6	400	20	20	5	10
T-7	450	20	20	5	15
T-8	400	20	20	5	20

Table no.02: Formulation of Microspheres

SPRAY DRYING:

Polymer is softened in a suitable instable solvent such as dichloromethane. Drug in the solid procedure is then range in the polymeric solution below high the high homogenization. Spreading is then atomised in a temperature of hot air.

Atomisation leads to formation of small drops or the fine vapour the Solvent evaporates suddenly to formation of microspheres.

SOLVENT EXTRACTION:

This technique is castoff in the making of the micro particles, involves exclusion of the phase by omission of the organic solvent. The method involves water soluble isopropanol. Process involves direct mixing of the drug or protein to organic solution. The degree of solvent deduction by removal on the heat of water, relation of emulsion quantity to the water and the soluble index of the polymer.

Materials and Methods:

Duloxetine Hydrochloride collected as gift sample from Sreepathi Pharmaceuticals Ltd., India. Microcrystalline cellulose from Thomas baker pvt ltd, Mumbai, sodium alginate from S.D. Fine chemicals Ltd., Mumbai, Methocel K 100 from Burgoyne laboratory; Mumbai, India and other excipients are collected from SD Fine chemicals.

Results and Discussion

Analytical method

Preparation of 0.1 N Hcl:

8.5 ml of concentrated HCl was taken and dilute with distilled water up 1000ml.

Determination of λ_{max} of Duloxetine HCl using 0.1 N HCl:

Procedure:

Working standard:

5mg of Duloxetine was taken and dispersed in 100 ml. 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 step is 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 λ_{max}

Construction of standardisation curve of Duloxetine HCl 0.1N Hcl

Procedure:

5mg of Duloxetine was weighing up and dissolved and then invented to a volume of 100ml with 0.1N HCL 50µg/ml stock solution.

Dilutions:

a. 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.

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

Table no.03: concentration of duloxetine

Y=0.014x+0.088
R2= 0.937

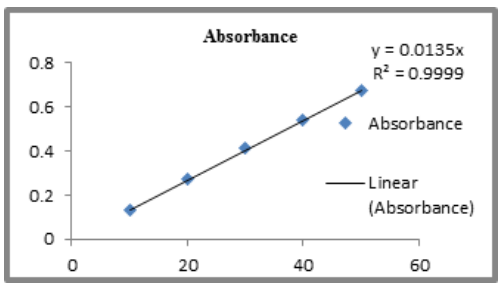


Figure no: 05 STANDARD GRAPH OF DULOXETINE HYDROCHLORIDE

FTIR COMPATABILITY STUDIES:

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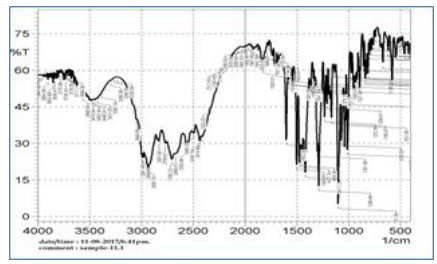

Figure no: 06 Duloxetine Hydrochloride FTIR Spectra

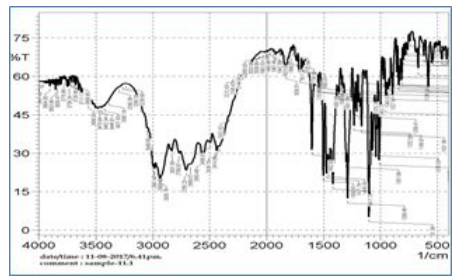

Figure no. 07: Duloxetine Hydrochloride with Sodium Alginate FTIR Spectra

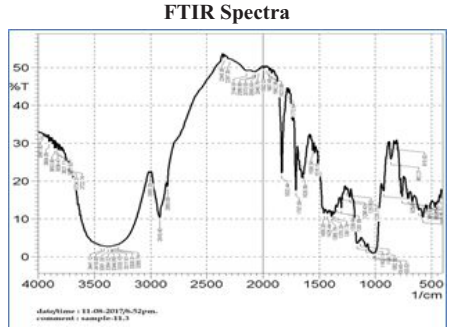

Figure no: 08 Duloxetine Hydrochloride with Methocel E-50 FTIR Spectra

FTIR studies indicate there is no much interaction between pure drug Duloxetine hydrochloride, sodium alginate and Methocel E-50 as referred in above graphs.

1. N-H starching vibrations close to 3400cm^{-1}
2. Naphthalene and thiopene groups having peaks orientation between 1600 and 1450cm^{-1}
3. Above said functional groups have no much interaction between sodium alginate and Methocel E-50

PHYSICAL CHARACTERIZATION OF MICROSPHERES:

	T-1	T-2	T-3	T-4	T-5	T-6	T-7	T-8
B.D	0.9	0.6	1.5	1.8	2	5.2	2.4	0.9
T.D	0.8	0.5	1.2	1.7	1.9	4.9	2	0.8
% YIELD	53.84	31.00	52.03	55.24	64.02	23.92	67.88	53.84

TABLE NO.04: PHYSICAL CHARACTERIZATION OF MICROSPHERES

DRUG RELEASE FROM DULOXATINE MICROSPHERES:

Time	T-1	T-2	T-3	T-4	T-5	T-6	T-7	T-8
0	0	0	0	0	0	0	0	0
30	2.12	5.57	3.14	6.21	4.79	5.29	4.64	11.64
60	4.43	7.79	15.76	6.36	6.57	6.36	6.43	15
90	6.07	3.21	5	6.29	5.71	6.29	15.45	21.23
120	5.64	5.79	34.19	6.14	6.29	6.21	24	29.26
150	39.29	28.86	14.54	8.57	9.07	8.64	36.12	35.65
180	17.71	32.87	23.43	7.21	7.71	7.21	49.23	45.87
240	45.67	34	14.65	24.76	15.23	10.23	57.31	52.87
300	35.56	76	23.67	43.78	34.33	13	66.12	62.67
360	78.98	43.87	15.42	42.18	39.35	21	78.23	72.34
420	75.67	40.65	10.45	54.67	45.35	6	82.43	82.12
480	77.84	75.66	45.89	76	73.29	34	95.23	93.35

Table no. 05: Drug release from trial 01 to trial 08

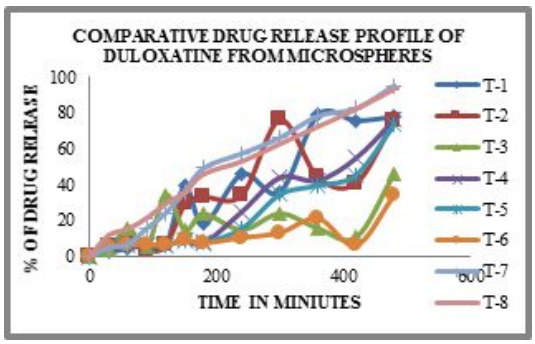

Figure No: 09 Comparative Drug Release For Mt-01 To T-08

One month stability studies of optimized formula trial-08:

Table no: 06 drug release from T-08-optimized and reproducible formula:

SL. NO	Time	% of drug release
	0	0
1	30	12.65
2	60	25.21
3	90	31.34
4	120	46.98
5	150	51.28
6	180	69.36
7	240	78.34
8	300	89.12
9	360	92.34
10	420	95.29
11	480	99.18

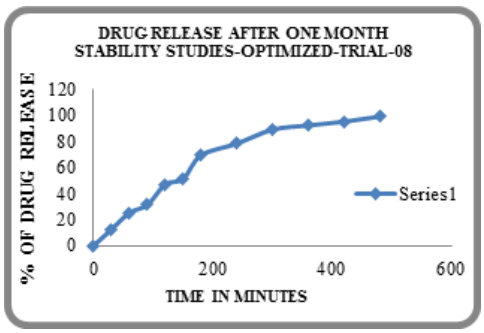

Figure no.10: graphical representation of drug release after one month stability studies

DETERMINATION OF RELEASE RATE KINETICS FOR OPTIMIZED FORMULA TRIAL -08

Zero Order		First Order		HIGUCHIS Model		KORESMEYER PEPPAS	
TIME	% Drug Undissolved	time	LOG 100-Q	Sqrt. time	mean % drug dissolved	log time	log cumulative % drug dissolved
0	100	0	2	0	0	0	0
30	87.35	30	1.94	5.48	12.65	1.48	0.17
60	74.79	60	1.87	7.75	25.21	1.78	0.25
90	68.66	90	1.84	9.49	31.34	1.95	0.29
120	53.02	120	1.72	10.95	46.98	2.08	0.32
150	48.72	150	1.69	12.25	51.28	2.18	0.34
180	30.64	180	1.49	13.42	69.36	2.26	0.35
240	21.66	240	1.34	15.49	78.34	2.38	0.38
300	10.88	300	1.04	17.32	89.12	2.48	0.39
360	7.66	360	0.88	18.97	92.34	2.56	0.41
420	4.71	420	0.67	20.49	95.29	2.62	0.42
480	0.82	480	0.09	21.91	99.18	2.68	0.43

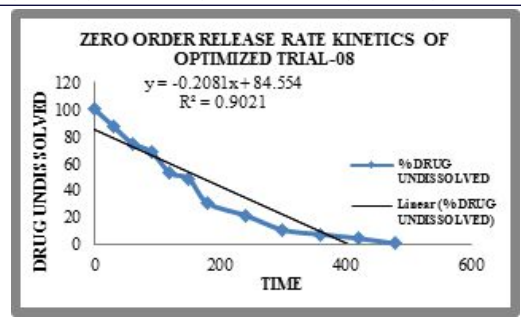

Figure no.11: Graphical representation of zero order kinetics of optimized trial-08

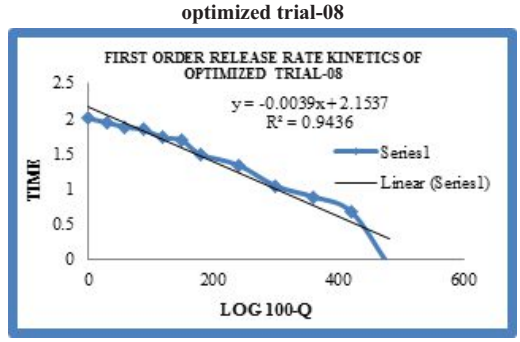

Figure no: 12 Graphical representation of first order kinetics of optimized trial-08

Zero Order

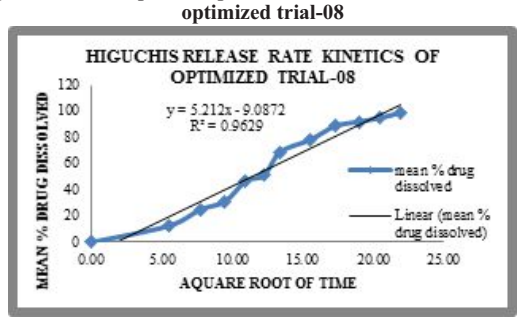

Figure no. 13: Graphical representation of HIGUCHIS MODEL kinetics of optimized trial-08

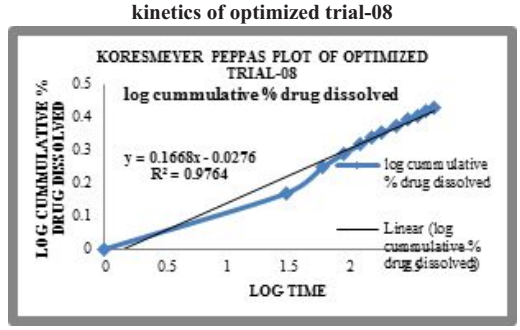

Figure no: 13 Graphical representation of KORESMEYER PEPPAS model kinetics of optimized trial-08

Discussion:

Excipients and API was selected base on the FTIR Studies.

A compatibility study according to the FTIR interpretation between the peaks of pure API duloxetine hydrochloride and other inactive ingredients were negligible interaction between them, and was selected for the formulation of duloxetine hydrochloride extended release microspheres.

All the in house prepared Duloxetine Microspheres were taken for drug release studies.

The release of drug from Microspheres of T1-T8 was found to be in increasing order with respect to time (T1-T8).

T8 was optimized bound upon the drug release and in-vitro evaluation parameters. T8 was selected as an optimized formula and taken for reproducible batch.

After aligning all the in-intro evaluation parameters within limits according to standard book it was taken for one month stability studies at accelerated stability conditions.

The drug release from optimized trial T-8 was determined for released rate kinetics for Zero order, First order , Higuchi's and Peppas method of which R^2 was found to be **0.9021** for Zero order kinetics, **0.9436** for First order, **0.9629** for Higuchi's and **0.9764** for Peppas model.

Conclusion:

With the drug release studies and all other in-vitro evaluation parameters formulation trial T-8 was optimized.

Based on the regression coefficient value it was determined and concluded that release from DULOXATINE HYDROCHLORIDE extended release microspheres was found to be following Koresmeyer Peppas model with regression coefficient value R^2 of 0.9764

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