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FORMULATION AND EVALUATION OF DULOXETINE FLOATING MICROPHERES

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ABSTRACT

The aim of study was formulate and evaluate floating microspheres of highly water soluble drug Duloxetine HCl, using cellulose acetate and eudragit RS100 polymers. The microspheres were prepared by solvent evaporation method. The prepared microsphere showed good drug loading capacity and floating ability. The particle size was ranged between 50 µm to 200 µm depends on the drug polymer ratio. The SEM study revealed that microspheres were good spherical geometry and uniform size. FT- IR studies of drug loading microspheres showed no interaction of drug and polymers. The *in vitro* re- lease studies were performed in 900 ml of 0.1N HCl for 12 h using USP XXIV dissolution apparatus. Release studies showed that microspheres that able to release the drug in sustain manner. Selected for- mulations were subjected to kinetics studies and stability studies. The release kinetics studies showed that the release the first order diffusion control and n value obtain from Higuchi model showed the re- lease mechanism. Stability studies indicated that developed microspheres were stable and retain their pharmaceutical properties at room temperature and 40ºc/75% RH of one month.

KEYWORDS: Venalfaxine, Eudragit, Dissolution.

1. INTRODUCTION

1.1 Introduction to floating drug delivery system[1,2]

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. The most convenient and commonly employed route of drug delivery has historically been by oral ingestion. Drugs that are easi- ly absorbed from the GIT and having a short half-life are eliminated quickly from the blood circulation. To avoid these problems oral controlled drug delivery systems have been developed as they releases the drug slowly into the GIT and maintain a constant drug concentration in the serum for longer period of time. However, incomplete release of the drug and a shorter residence time of dosage forms in the up- per gastrointestinal tract, a prominent site for absorption of many drugs, will lead to lower bioavailabil- ity. Efforts to improve oral drug bioavailability have grown in parallel with the pharmaceutical indus- try. As the number and chemical diversity of drugs has increased, new strategies are required to devel- op orally active therapeutics. Thus, gastro retentive dosage forms, which prolong the residence time of the drugs in the stomach and improve their bioavailability, have been developed.

1.1.1 Gastro-retentive drug delivery systems/gastro-retentive dosage forms (GRDFS)[3,4]

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time i.e. Gastro retentive Dosage Forms (GRDFs) These are primarily controlled release drug delivery systems, which gets retained in the stomach for longer periods of time, thus helping in absorption of drug for the intended duration of time. Gastric retentive drug delivery devices can be useful for the spatial and temporal delivery of many drugs. Thus, control of placement of a DDS in a specific region of the GI tract offers numerous advantages, especially for drug exhibiting an 'absorption window' in the GI track. The intimate contact of the DDS with the ab- sorbing membrane and also the potential to maximize drug absorption may influence the rate of drug absorption. These considerations have led to the development of oral controlled release (CR) dosage forms possessing gastric retention capabilities. Drug may not be absorbed uniformly over the length of the gastrointestinal tract, because dosage form may be rapidly transported from more absorptive upper regions of the intestine to lower regions where the drug is less absorbed and drug absorption from colon is usually erratic and inefficient. Moreover, certain drugs are

absorbed only from the stomach or the upper part of small intestine.

1.1.2 Methods for gastro-retentive drug delivery systems[5]

1.1.2.1 Bio/Mucoadhesive systems

The term bioadhesion describe materials that bind to the biological substrates, such as mucosal mem- brane. Adhesion of bioadhesive drug delivery devices to the mucosal tissue offers the possibility of cre- ating an intimate and prolonged contact at the site of administration. This prolonged residence time can result in the enhanced absorption and in combination with a controlled release of drug also improved patient compliance by reducing the frequency of administration. The epithelial adhesive properties of mucin have been applied in the development of gastro retentive drug delivery systems.

1.1.2.2 Floating systems

Floating systems are low-density systems that have sufficient buoyancy to float over the gastric con- tents and remain in the stomach for a prolonged period. While the system floats over the gastric con- tents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation in plasma drug concentration.

1.1.2.3 Swelling systems

These are capable of swelling to a size that prevents their passage through the pylorus; as a result, the dosage form is retained in the stomach for a longer period of time. Upon coming in contact with gastric fluid, the polymer imbibes water and swells.

1.2 Approach of the gastric retention[6]

A number of approaches have been used to increase gastric retention time (GRT) of a dosage form in stomach by employing a variety of concepts. These includes in this **figure1.1.**

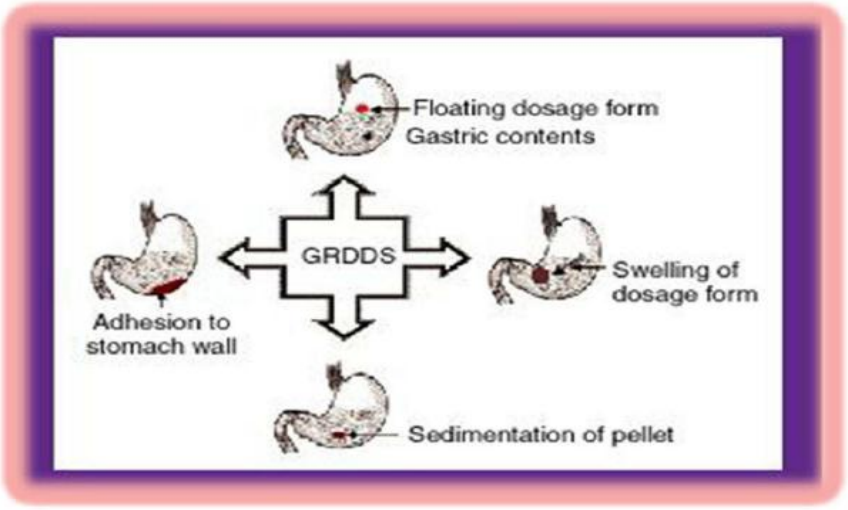

Figure 1.1: Approach of the gastric retention.

1.3 Factors controlling gastric retention of dosage form[7]

The stomach anatomy and physiology contain parameters to be considered in the development of gastro retentive dosage forms. To pass through the pyloric valve in to the small intestine the particle size should be in the range of 1 to 2 mm. The most important parameters controlling the gastric retention time (GRT) of oral dosage forms include : density, size and shape of the dosage form, food intake and its nature, caloric content and frequency of intake, posture, gender, age, sex, sleep, body mass index, physical activity and diseased states of the individual (e.g. chronic disease, diabetes etc.) and admin- istration of drugs with impact on gastrointestinal transit time for example drugs acting as anticholiner- gic agents (e.g. atropine, propantheline), Opiates (e.g. codeine) andprokinetic agents (e.g. metclopramide, cisapride.). The molecular weight and lipophilicity of the drug depending on its ioniza- tion state are also important parameters.

2. MATERIALS AND METHODOLOGY

Materials

Duloxetine hcl was gifted by Amoli organics pvt. ltd, Cellulose Acetate – National chemical (Baroda),– National chemicals (Baroda), Eudragit RS 100 – Suvidhinath laboratories (Baroda). All other chemi- cals used were of analytical grade.

3. RESULT AND DISCUSSION

3.1 Solubility profile of duloxetine hydrochloride

The solubility of Duloxetine hydrochloride was tested in various common solvents qualitatively. A definite quantity (10 mg) of the drug was dissolved in 10 ml of each investigated solvent at room tem- perature in tightly closed glass test tubes. solubility of Duloxetine HCl shown in **Table 5.1**

Table 5.1: Solubility profile of duloxetine hydrochloride.

Sr. No	Solvent	Solubility
1	Distilled water	Soluble
2	Methanol	Freely soluble
3	Anhydrous Ethanol	Sparingly soluble
4	Acetone	Practically insoluble
5	Dichloromethane	Practically soluble

3.2 Preparation of standard curve

10 mg of Duloxetine hydrochloride was weighed accurately and dissolved in 0.1 N hydrochloric acid in a 100 ml of volumetric flask and volume was made up to the mark with the 0.1 N hydrochloric acid. The concentration of this standard stock solution was 100 □g/ml. From this stock solution, aliquots of 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, 6 ml, were transferred to 10 ml volumetric flasks and volume was made up to 10 ml with 0.1 N hydrochloric acid. The absorbance of these solutions was measured at 226 nm against a blank 0.1 N hydrochloric acid. The plot of absorbance v/s concentration (µg/ml) was plotted and data was subjected to linear regression analysis in Microsoft Excel.

Table 5.2: Calibration curve of Duloxetine HCl in 0.1 N HCl at 226 nm.

Sr. No	Concentration (□g/ ml)	Absorbance± SD*
1	10	0.097±0.002
2	20	0.216±0.003
3	30	0.354±0.01
4	40	0.468±0.002
5	50	0.573±0.005
6	60	0.667±0.005

*n=3

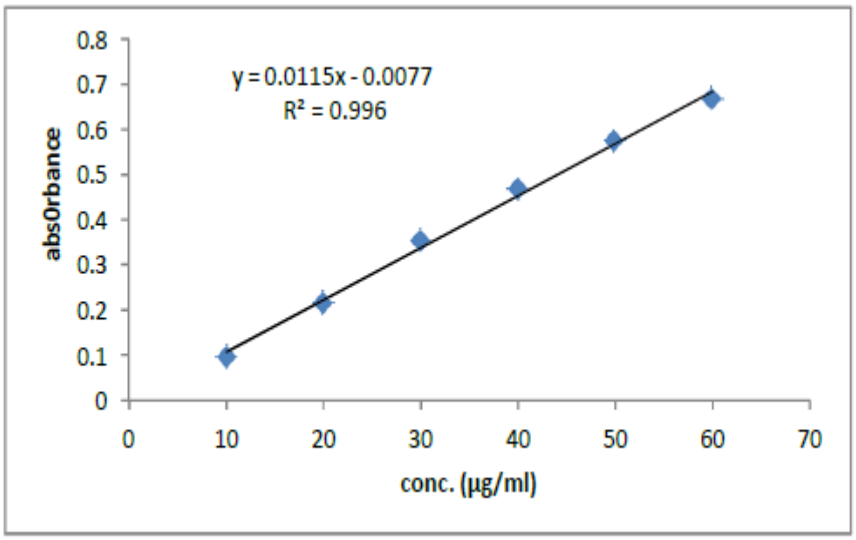

Figure 5.2: Calibration curve of Duloxetine HCl in 0.1 N HCl at 226 nm.

3.3 Determination of melting point

Melting point of Duloxetine hydrochloride was found 2150C respectively.

3.4 *In vitro* drug release study

3.4.1 In vitro drug release of prepared microspheres

The *in vitro* release study of drug Duloxetine HCl from the various microspheres formulation market- ed floating tablet were carried out by using USP XXIV dissolution apparatus type I in 0.1 N HCl in pH 1.2 separately for 1 to 12 hr respectively. Cumulative % release of different formulation is show in.

Table 5.7: Cumulative% release of following batches.

Sr. no	Time (hr)	Cumulative% release±SD*					
		F1	F2	F3	F4	F5	F6
1	0.5	20.54±1.28	12.23±1.12	19.45±1.22	14.25±1.52	12.59±0.95	7.05±1.97
2	1	35.99±0.90	24.39±1.67	35.37±0.99	29.39±1.32	28.14±1.24	16.73±1.31
3	2	45.49±0.98	34.95±1.98	41.57±1.22	37.95±1.88	34.82±1.32	21.82±1.94
4	3	54.35±1.54	39.92±1.87	47.24±1.63	42.96±1.67	39.69±1.44	26.64±1.22
5	4	63.03±2.21	46.15±1.44	56.35±2.21	49.15±1.44	46.98±1.54	30.26±0.87
6	5	72.14±1.20	50.13±1.67	62.18±0.95	52.13±1.24	53.16±1.31	35.66±1.03
7	6	80.61±1.02	54.45±1.23	67.24±1.51	55.99±1.65	55.26±2.31	41.44±1.96
8	8	92.13±0.89	64.03±1.43	86.49±1.99	67.03±1.97	67.12±1.94	54.22±2.21
9	10	93.54±1.44	81.31±1.98	93.59±1.46	82.31±2.01	80.20±0.93	63.22±2.09
10	12	93.48±2.22	92.65±2.11	94.28±2.33	94.75±2.61	88.13±0.91	74.59±0.99

*n=3

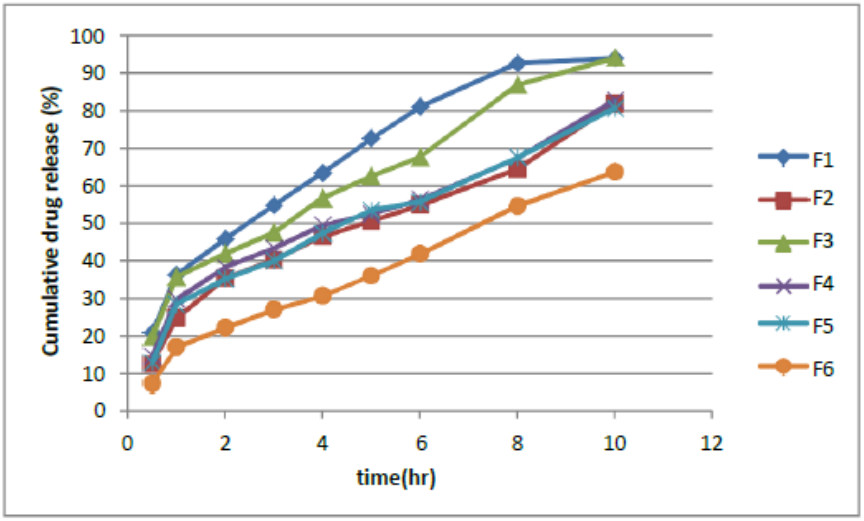

Figure 5.7: Comparative drug release study of prepared Microspheres and Marketed product.

3.5 Characterization of microspheres

Table 5.8: Data of characterization of the microspheres.

Batch Code	Process Yield (%)	Mean parti- cle size (µm) ±SD*	Bulk den- sity (gm/mL) ±SD *	Carr's index±SD *	Hausner 's ration±SD *	Angle of re- pose±SD *
Duloxetine HCl	–	–	0.175 ± 0.01	26.47± 0.16	1.36 ± 0.07	–
F1	80.28	101.36 ± 2.26	0.294 ± 0.02	5.77 ± 0.12	1.06 ± 0.02	21.81 ± 0.22
F2	82.13	107.22 ± 2.26	0.289 ±0.01	7.12 ± 0.15	1.07 ± 0.02	21.98 ± 0.28
F3	85.4	116.75 ± 2.03	0.286 ± 0.02	8.33 ± 0.37	1.09 ± 0.08	23.27 ± 0.56
F4	86.09	122.56 ± 3.22	0.286 ± 0.01	11.18 ± 0.26	1.12 ± 0.06	23.74 ± 0.45
F5	88.27	135.47 ± 1.89	0.278 ± 0.03	13.66 ± 0.19	1.15 ± 0.04	24.70 ± 0.59
F6	91.86	142.01 ± 2.21	0.270 ± 0.04	13.51 ± 0.09	1.19 ± 0.09	26.56 ± 0.19

*n=3

Note: _ the particular test not carried for Duloxetine HCl

3.6 Drug entrapment efficiency and % buoyancy at 12hr

Table 5.9: Data of drug entrapment and % buoyancy.

Formulation Coad	Drug entrapment Efficiency(%)±SD*	Buoyancy at 12hr (%)±SD*
F1	52.78±0.11	62.7±0.1
F3	60.35±0.09	55.6±0.05
F4	62.92±0.08	64.8±0.08
F5	61.34±0.09	61.8±0.05
F6	60.61±0.10	63.6±0.09

* n=3

3.7 Speed optimization of selected formulation and result

Table 5.10 Speed optimization of selected Formulation and Result.

Sr. no.	Batch	Speed(rpm)	Result
1	$F4_1$	500	Not spherical
2	$F4_2$	1000	Spherical
3	$F4_3$	1500	Spherical
4	$F4_4$	2000	Not spherical

3.8 Surface topography (SEM)

The surface morphology, shape and to confirm the hollow nature, microspheres were analyzed by scan- ning electron microscopy for selected batches F1 to F4 (Leo, VP-435, Cambridge, UK). Photomicro- graphs were observed at required magnification operated with an acceleration voltage of 15 kV and working distance of 19 mm was maintained. Microspheres were mounted on the standard specimen- mounting stubs and were coated with a thin layer (20 nm) of gold by a sputter-coater unit to make the surface conductive. (VG Microtech, Uckfield, UK).

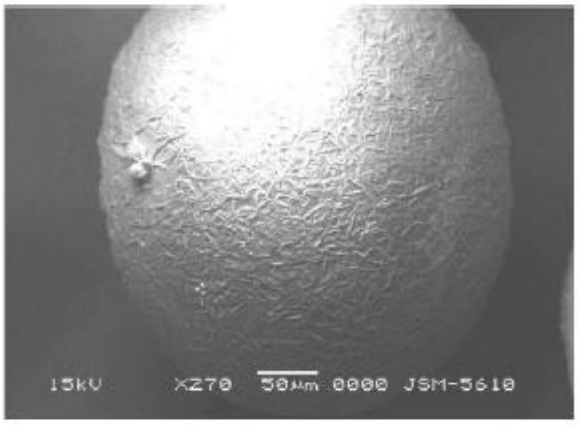

Figure 5.10: SEM Photographs of Floating Microspheres of selected F4 batch.

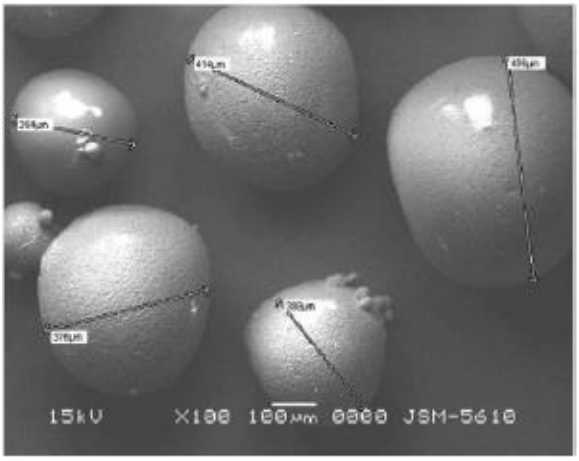

Figure 5.11: SEM Photographs of Floating Microspheres of selected F4 batch.

3.9 Kinetic data of drug release from various formulations

Table 5.11: Kinetic data of drug release from various formulations.

Batch Code	Zero order		First order		Higuchi's kinetics	
	Rate Constant (K) mg. min^{-1}	Regres- sion coefficient (R^2)	Rate Constant (K) mg. min^{-1}	Regres- sion Coeffi- cient (R^2)	Rate con- stant (K) mg. min^{-1}	Regression coefficient (R^2)
F_1	5.545	0.8900	0.038	0.8438	25.911	0.9550
F_2	5.613	0.9231	0.041	0.8952	26.118	0.9623
F_3	5.543	0.9601	0.040	0.9300	26.558	0.9750
F_4	5.704	0.9912	0.044	0.9734	25.31	0.9596
F_5	5.706	0.9940	0.043	0.9701	26.44	0.9715
F_6	5.709	0.9981	0.042	0.9661	26.01	0.9693

3.10 Release kinetics and release mechanism of formulation F4

Table 5.12: Release kinetics of formulation F4.

Time (h)	Square root of Time	Log time	%CDR	Log of %CDR	Log Cu% of drug remaining
0.5	0.707	-0.301	14.25	1.153	1.933
1	1	0	29.39	1.468	1.848
2	1.414	0.301	37.95	1.568	1.792
3	1.732	0.477	42.96	1.633	1.756
4	2	0.602	49.15	1.691	1.706
6	2.449	0.778	55.99	1.748	1.643
8	2.828	0.903	67.03	1.826	1.518
10	3.162	1	82.31	1.915	1.247
12	3.464	1.079	94.75	1.976	0.720

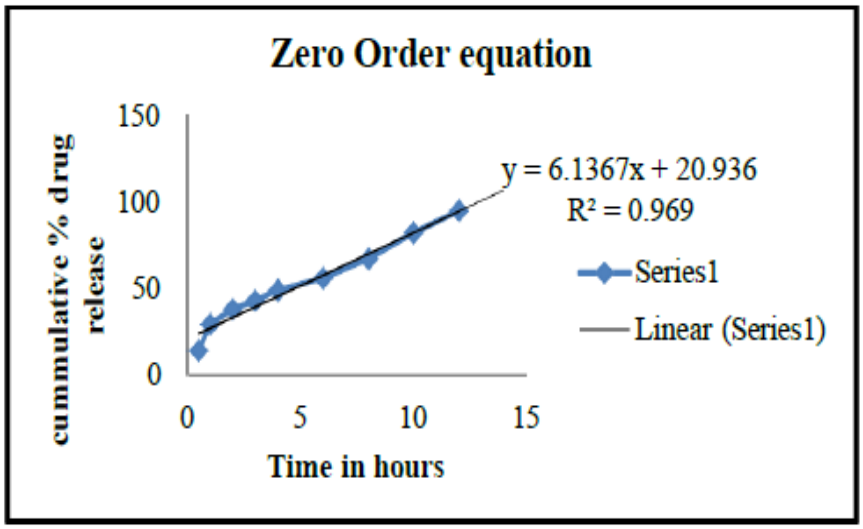

Figure 5.11: Zero order release kinetics of formulation F4.

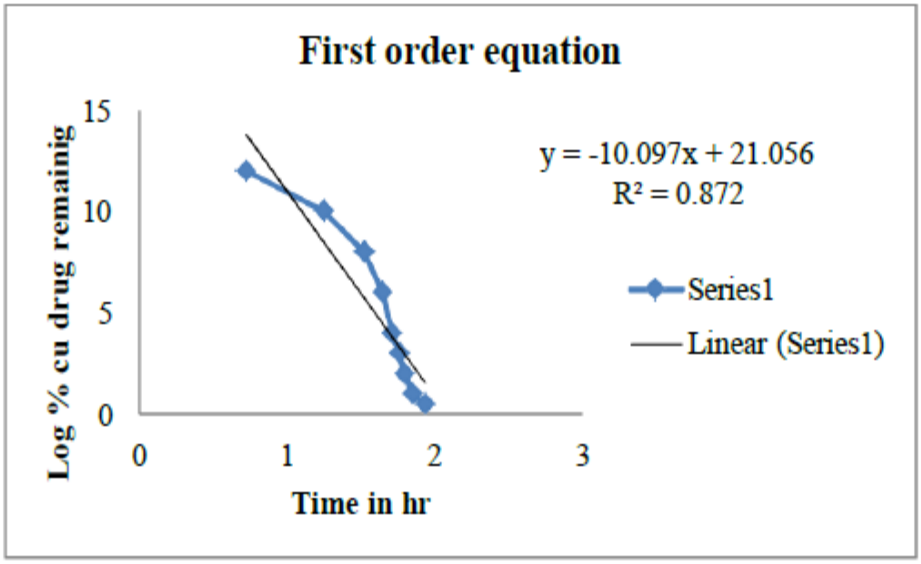

Figure 5.12: First order release kinetics of formulation F4.

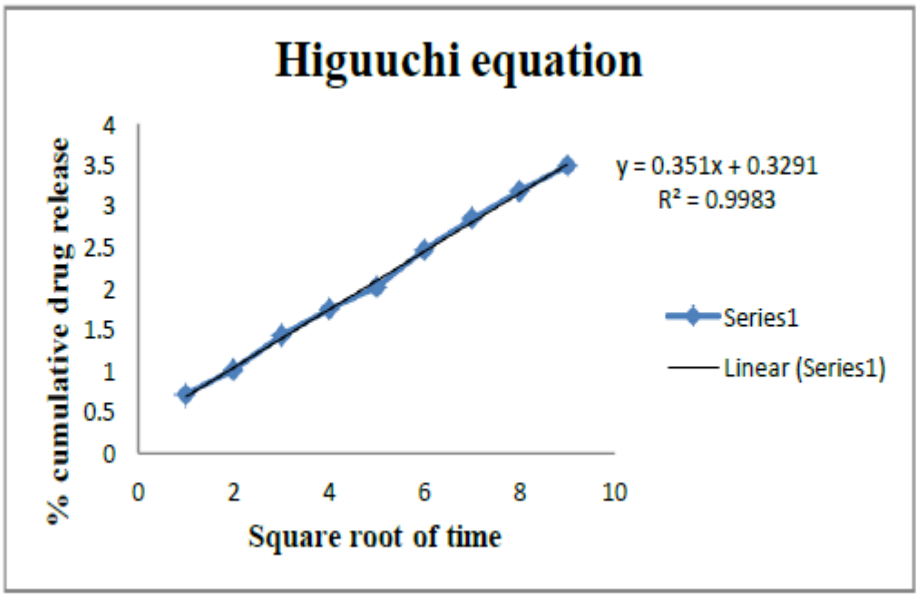

Figure 5.13: Higuchi model release kinetics of formulation F4.

3.11Data of stability studies of Formulation F4.

Table 5.12: Data of stability studies of Formulation F4.

Evaluation Parameter	Observation in day±SD*						
	Initial	Room temperature			40 ± 1ºC/75%RH		
		10	20	30	10	20	30
Physical appearance	White colour	No Change	No Change	No Change	No Change	No Change	No Change
FT-IR pattern	Performed	_	_	No Change	_	_	No Change
Drug Content* (%W/W)	100	99.65 ± 0.06	99.59 ± 0.08	99.53 ± 0.05	99.84 ± 0.11	99.38 ± 0.09	99.62 ± 0.13
%CDR*	94.75 ± 0.14	94.55 ± 0.13	94.43 ± 0.09	94.21 ± 0.62	94.24 ± 0.07	94.10 ± 0.16	93.80 ± 0.55

*n=3

4. DISCUSSION

4.1 Preformulation studies

In the first phase of our study, the drug were subjected to preformulation studies namely the drug- polymer compatibility study, solubility, melting point. Drug-polymer interaction were studied using FT-IR analysis and showed that no changes IR spectrum of pure Duloxetine HCl in presence of kol- lidon SR and cellulose acetate(Table 5.6, figure 5.2-5.5), which shows that the polymer do not alter the performance characteristics of drug, the revealing compatibility of selected drug with polymer.

The solubility studies of Duloxetine HCl in different solvent. Duloxetine HCl is highly water soluble and soluble in methanol, anhydrous ethanol. The melting point of Duloxetine HCl was found to be 215ºC.

4.2 Preparation of microspheres

In present studies, floating microspheres of Duloxetine HCl prepared by solvent evaporation technique with different drug pokymer ratio. Liquid paraffin and (DCM and methanol) system was used for prep- aration of microspheres. The procedure used for preparation microspheres produce good yield, which indicate minimum loss of microspheres during the preparation and recovery.

4.3 Characterization of microspheres

4.3.1 Process yield

The process yield if Eudragit RS 100 and cellulose acetate microspheres of drug Duloxetine HCl (F1, F3-F6) was found to be range of 80.28 to 91.26 (Table 5.8). the large surface area of the partials and water solubility of drug the two key factor which accelerate drug loss into the aqueous phase during microspheres preparation.

4.3.2 Particle size

The mean particle size of microspheres was found to be in a range of 101.36 ± 2.26 to 142.01 ± 2.21 µm (Table 5.8). the surface morphology of drug loaded microspheres was studied by scanning electron microscopy and study revealed that microspheres was spherical in shape and uniform in size(figure)

4.3.3 Micromeritics properties of microspheres

The drug loaded microspheres was evaluated for bulk density, carr's index, and angle of repose(Table) The flow characteristics of microspheres was assessed by determining carr's index and angle of repose. The carr's index and angle of repose of microspheres was less than 15 and 28º respectively, which indi- cate excellent flow compare to pure druga, also microspheres was found exhibit higher packing proper- ties (Hauser's ratio) than the pure drug.

4.3.4 Drug entrapment efficiency and % buoyancy at 12 hr

The drug entrapment efficiency was in the range of 52.71% to 60.61% and % bouancy at 12 hr range to 55.6% to 64.8% respectively. The drug entrapment effiuciancy and % bouancy of microspheres de- crease with increase concentration of eudragit RS 100.

4.3.5 FT-IR spectroscopy studies on drug loaded microspheres

The possible drug-polymers interaction during the time of preparation was studied using FT-IR analysis and showed that there was no significant changes in IR spectra of drug loaded microspheres contain Duloxetine HCl. The result suggest that the drug's stability was not affected during encapsulation pro- cess.

4.3.6 *In vitro* drug release studies

The in vitro release data of all formulations were also subjected to model fitting analysis to know the mechanism of drug release from the formulations by treating the data according to zero order, first or- der, Higuchi equation. The results are shown in Table.5.7. It can be interpreted from the result that the release of drug from the microspheres followed zero order kinetics. Further, the higuchi plot revealed that the drug release from the microspheres obeyed diffusion mechanism. It can be concluded that the formulation of microspheres (F4) containing Duloxetine HCL and cellulose acetate and Eudragit RS 100 (1:2) seems to be promising and release data of F4 batch was comparatively best than other batches based on comparative studies with marketed product.

4.3.7 Stability studies

Stability studies for all formulations were performed for three months, at room temperature (25 ± 2ºC), and at 40ºC / RH 75 %. The floating microspheres were stored at various above mentioned tempera- tures. Stability profile of different formulations at various temperatures is shown in Table 5.12. The da- ta depicts that the floating microspheres stored at room temperature, refrigeration temperature, were found to be comparatively stable and at 40ºC / RH 75 % there was less than 4% degradation at the end of one months.

5. CONCLUSION

In present study, an attempt was to made to developmultiparticulate delivery system (microspheres) for highly water soluble drug Duloxetine HCl.

The possible drug-polymers interaction during the time of preparation was studied using FT-IR analysis and showed that there was no significant interaction between drug and polymers.

Eudragit RS 100 and cellulose acetate microspheres of Duloxetine HCl was prepared by solvent evapo- ration techniques. The method is able to produce spherical particles with uniform size and free flowing nature.

All the formulations showed highly process yield and drug encapsulation efficiency. Among different batches, formulation F4 was selected ideal formulation, after

consider their mean particle size, free flowing nature, better drug loading capacity and *in vitro* drug release studied compare with marketed product.

Release kinetics studies showed that Duloxetine HCl release from the microspheres were better fitted to zero order and Haguchimodel indicate r2. Which indicate drug release was zero order diffusion con- trol.

The speed optimization of particular F4 batch on different four speed on mechanical stirrer after formulation, based on spherical shape F42 batch is best spherical shape as compare to other. Particle size range was 150µm was the best size achieve as per our requirement.

The ideal formulation F4 was subjected to stability studies at room temperature and 40ºC/75%±RH. The stability study indicated that the formulation was stable and retain their pharmaceutical properties at room temperature and 40ºC/75%±RH over period of one month.

Based on observation, it can be conclude that the formulated multiparticulate delivery system (microspheres) of highly water soluble drug Duloxetine HCl and physiological safe polymer like Eudragit RS 100 and cellulose acetate were capable of exhibiting sustain release properties for period of 12 hr. They are thus may be reduce frequency of dosing, there by minimize side effects, and increase effectiveness of drug.

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