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DESIGN, DEVEOPMENT AND EVALUATION OF BILAYER FLOATING TABLET OF DRUG DULOXETINE (DL)

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Abstract

Controlled release tablets were prepared by different approaches using different polymers, individually or mixture. All the designed formulations were evaluated for their drug content, weight variation, hardness, friability and in vitro release profile. Preformulation studies indicated that Duloxetine (DL) was non-hygroscopic, poor flowing and highly soluble between pH 1.2 to 10. Solid state stability studies showed that Duloxetine (DL) was stable and compatible with various excipients for sufficient time period. In addition, DSC and FTIR studies also indicated the compatibility of Duloxetine (DL) with excipients used for controlled release formulations. Controlled release formulations were prepared using hydrophilic polymers (HPMC 15K, HPMC 100K, sodium CMC, carbopol) alone or in combination using wet granulation process. Multi granules based CR tablets were prepared with mixing the granules of hydrophilic polymers and hydrophobic polymers in different proportions. The quality control parameters of all the formulations were found to be satisfactory and within the official pharmacopoeial limits suggesting used process can produce good quality products.

Keyword: Duloxetine (Dl), Preformulation Studies, Characterization, Results

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1. Introduction :

Duloxetine is a serotonin–norepinephrine reuptake inhibitor (SNRI) used in the clinical treatment of major depressive disorder [1] and fibromyalgia [2]. It has been approved since late 1990s in some European and Asian countries for the treatment of depression and has now also been approved for the treatment of fibromyalgia [3-4].

Depression is mean to intense and prolonged sadness. Sadness is an emotion that everyone feels at some time or other, often in response to bereavement, illness or loss. However, depression (also referred to as clinical depression) is different from just feeling sad. Depression is a mood disorder, also called an affective disorder. Depressive signs and symptoms are characterize not only by negative thoughts, moods, and behaviors but also by specific changes in bodily functions such as, crying spells, body aches, low energy or libido, as well as unwillingness for eating, weight loss, or sleeping. The functional changes of clinical depression are often called neurovegetative signs. This means that the nervous system gets changed, cause many physical symptoms that result in diminished participation and a decreased activity level [5-6].

The monoamine hypothesis of depression postulates that the underlying pathophysiologic basis of depression is depletion in the levels of serotonin, norepinephrine, and/or dopamine neurotransmission in the brain. This hypothesized pathophysiology supported by the mechanism of action of current antidepressants that elevated the levels of these neurotransmitters in the brain for patients whose depression was caused by the imbalance of either norepinephrine or serotonin.

Fibromyalgia (FM) is a rheumatologic disorder characterized by widespread musculoskeletal pain and lowered pain threshold. Other prominent symptoms include stiffness, paresthesias, disturbed sleep, fatigue, psychologic distress and tenderness at predefined anatomic sites. Due to these multiple symptoms and high rates of comorbidity with other related disorders, patients with FM often report a reduced quality of life [7].

The etiology and pathophysiology of FM are unclear. Although FM was previously thought to be a muscle disease, it is now considered a disorder of central

nervous system perception and regulation of pain [7]. In the central nervous system, both serotonin and norepinephrine have been found to play important roles in pain perception via their involvement in descending antinociceptive pathways. Dysfunction in these descending pathways is thought to result in the allodynic (painful response to nonpainful stimuli) and hyperalgesic (heightened sensitivity to pain) states experienced by patients with FM [8].

The goal of any drug delivery systems 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. Two aspects are most important to drug delivery, namely spatial placement and temporal delivery of a drug[4]. Spatial placement related to targeting drug to a specific organ or tissue. While temporal delivery refers to controlling the rate of drug delivery to the target tissue. The objective of this study was to develop an optimized GFDDS containing sustained release & immediate release model drug—a peroral intragastric floating dosage form having a bulk density lower than that of gastric fluids and remaining buoyant on the stomach contents.

To achieve the objectives, independent formulation variables like total polymer content-to-drug ratio, polymer-to-polymer ratio, and different viscosity grades of polymers will be use.

2. Material and Methods

Preparation of Reagents

Preparation of 0.1N HCL

8.5 ml of Con.HCl dissolved in 1000ml of distilled water to prepare a 0.1N HCl.

Stimulated Gastric Fluid pH 1.2

0.2 gm sodium chloride and 0.7ml of concentrated hydrochloric acid were mixed, to this mixture 1000ml distilled water are added and the solution was adjusted to pH 1.2 with sodium hydroxide solution.

ABSORPTION MAXIMA AND STANDARD PLOTS

Preparation of Absorption maxima for Duloxetine (DL) using pH 1.2

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stimulated gastric fluid.

Accurately weighed amount of Duloxetine (DL) (100 mg) was dissolved in small quantity of stimulated gastric fluid pH 1.2 and then diluted to 100 ml with the same solvent. Each ml of the stock solution contains 1 mg of Duloxetine (DL) . From this stock solution different standard of working standard solutions i.e., 10, 20, 30, 40, 50 □ g/ml were made up with stimulated gastricfluid pH 1.2 and the absorbance was measured at 232nm using stimulated gastric fluid as blank by UV spectroscopic method[47]. A graph was plotted by using concentration at X-axis and absorbance at Y-axis.

Absorption maxima and UV spectrum of Duloxetine (DL)

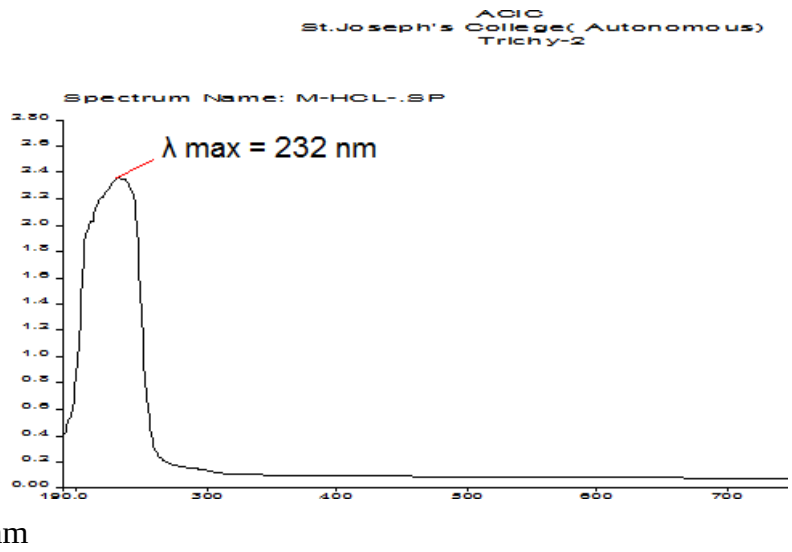

Fig :1 Absorption maxima and UV spectrum of Duloxetine (DL)

Standard Plot

Standard plot of Duloxetine (DL) in stimulated gastric fluid pH 1.2

Table No: 1

Standard plot of Duloxetine (DL)

S.No	Concentration µg/ml	Absorbance at 232nm
1	0	0
2	10	0.2897
3	20	0.5371
4	30	0.8484
5	40	1.118
6	50	1.39

RESULTS AND DISCUSSION

Preformulation studies

Description

Duloxetine (DL) : White to off white crystalline powder

Drug- Excipient Compatibility Studies by FT-IR analysis

Drug-Excipient compatibility was carried out by FT-IR analysis. Initially the IR spectrum of pure drug, **Duloxetine (DL)** and excipients like HPMC K4M, HPMC E-5 and HPMC E-15 was obtained. After that various admixtures of drug with

other excipients like **Duloxetine (DL)** , HPMC K4M, HPMC E-5 and HPMC E-15 were prepared and IR spectra were obtained. The obtained spectra of physical admixtures were observed for major peaks and recorded.

In **Duloxetine (DL)** drug was noticed that C-N stretching at 3303.04 and C- H stretching at 2692.21 In **combination of both the drugs** (**Duloxetine (DL)**) C-N stretching at 3289.10, C-H stretching at 2856.80 and C-H(out of plane) at 798.49.

In **Duloxetine (DL)** was noticed that C-H stretching at 3171.90 In **combination of Duloxetine (DL) and Polymer** were admixture and followed the same group in C-H stretching at 2939.64, 2944.65, 2940.92 and C-H aliphatic stretching at 2213.68, 2497.21, 2202.74.

In **Duloxetine (DL)** was noticed that N-H stretching at 3376.04 In **combination of Metformin HCl and Polymer** were admixture and followed the same group in N-H stretching at 3375.06,3385.45,3383.44 C=S stretching at1442.18, 1446.64,1451.54.

In **Duloxetine (DL)** was noticed that C-H out of plane at 931.65 In **combination of Duloxetine (DL) and Polymer** were admixture and followed the same group in C-H out of plane at 936.80, 939.58,937 S=O stretching at 1351.27

Table No : 2

IR Spectral assignment of Duloxetine (DL)

S.no	Wavenumber (cm^{-1})	Assignment
1	3173.06	N-H stretching
2	2687.10	C-H stretching

3	1629.52	C=O stretching
4	1573.03	C-N stretching
5	1168.15	C-C stretching
6	931.12	C-H out plane bending

EVALUATION PARAMETER

Evaluation of granules of Floating Duloxetine (DL) SR

The prepared granules were subjected to Pre-Compression parameters and the values are found to be within limits (Carr's index< 15% indicate excellent compressibility, Angle of repose<25° and Hausner's ratio<1.25 indicates good flow property). The results of granules were shown in the table no (31).

Table No : 3

Precompression parameters of Floating Duloxetine (DL) SR

Formulation batch code	Angle of repose (°) ± S.D	Bulk density (gm) ± S.D	Tapped density (gm) ± S.D	Carr's Index (%) ± S.D	Hausner's Ratio ± S.D
M4	23.98±0.3	0.49±0.05	0.59±0.01	14.82±0.56	1.02±0.4
M8	24.34±0.2	0.54±0.03	0.61±0.03	13.92±0.67	1.04±0.3
M12	26.59±0.4	0.56±0.02	0.62±0.02	15.01±0.28	1.11±0.6

S.D = Standard Deviation, n=3

Physical Evaluation of Floating Duloxetine (DL) **SR tablet**

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All the formulated tablets of trial batch (M4,M8&M12) would lies within the Pharmacopoecial limits. The uniformity of weight lies between 0.640-0.690g, friability (0.3-0.5%), drug content (98.98-99.99%), hardness (4-6Kg/cm^2) and Floating lag time was found to be 29,28&25secs. The 29and 28secs of M4&M8 formulation indicates that the low viscosity grade polymer HPMCE-15 shows maximum floating lag time and 25secs of M12 indicates the high viscosity polymerHPMCK4M shows minimum floating lag time. The values are tabulated in the following table no(32).

Table No: 4

Physico – Chemical Characteristics of Floating Duloxetine (DL) SR

Formulation batch code	Average weight of tablets(g) □ S.D	Hardness (Kg/cm^2) □ S.D	Friability (%) □ S.D	Drug content (%) □ S.D	Floating lag time (Secs)	Total buoyancy time (Hrs)
M4	0.651 □ 0.014	4.2□ 0.2	0.29□ 0.06	98.26□ 0.41	29□ 0.01	20
M8	0.649□ 0.022	4.8□ 0.1	0.3□ 0.04	98.99□ 0.52	28□ 0.23	20
M12	0.650□ 0.011	4.1□ 0.3	0.2□ 0.01	99.99□ 0.12	25□ 0.12	20

S.D = Standard Deviation, n=3

Table No:5

Determination of Swelling index for Floating Duloxetine (DL) SR

Time (hrs)	Formulation code		
	M4	M8	M12

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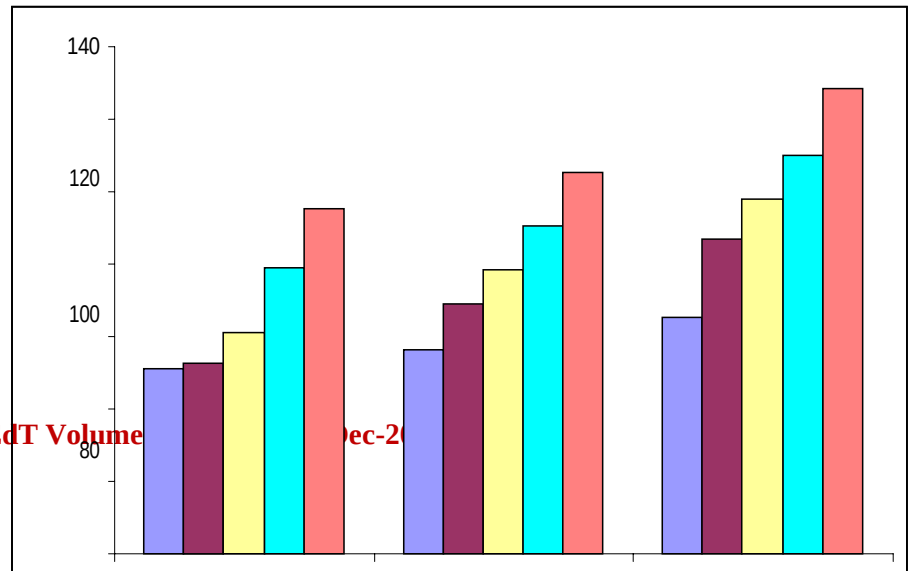
1	50.83±0.5	56.55±0.2	65.50±0.26
2	52.44±0.4	68.74±0.7	86.75±0.75
3	61.12±0.1	78.56±0.6	97.82±0.28
4	79.03±0.3	90.52±0.5	109.89±0.9
5	95.23±0.26	105.23±0.3	128.55±0.5

The formulation M12 shows the higher swelling index this is due to the viscosity of the polymer had major effect on swelling process. From the above, it was clear that swelling of tablet with increase in time passes because the polymer gradually absorbed water due to hydrophilic in nature and swell, the water

absorption rate increases as the viscosity of the polymer increases. At the end, the polymer of the higher viscosity shows the maximum absorption. It was shown in above table no(33).

Fig : 2

Determination of Swelling index for Floating Duloxetine (DL) SR



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In vitro drug release profile

The *in vitro* drug release study was carried out by using USP dissolution apparatus II (paddle type) and results were tabulated in the table (34).

Table No: 6

***In vitro* drug release of Floating Duloxetine (DL) SR**

Time (hrs)	Cumulative % of drug released (±S.D)		
	M4	**M8**	**M12**
0	0	0	0
0.25	4.31±0.31	5.07±0.73	6.59±0.52
0.5	9.66±0.60	9.15±0.12	14.55±0.58
1	13.54±0.54	13.01±0.14	18.59±0.54
2	18.85±0.86	17.82±0.86	27.96±0.94
4	24.15±0.12	22.46±0.42	33.11±0.19
6	30.57±0.56	27.28±0.29	41.24±0.26
8	37.99±0.98	31.03±0.34	47.13±0.14
10	43.31±0.31	36.17±0.13	53.98±0.96
12	48.92±0.99	40.98±0.92	61.18±0.12
14	53.68±0.67	49.69±0.63	67.24±0.24
16	61.79±0.75	54.33±0.34	75.67±0.64
18	66.09±0.96	60.78±0.76	83.24±0.23
20	70.8±0.82	66.19±0.18	**86.12±0.19**

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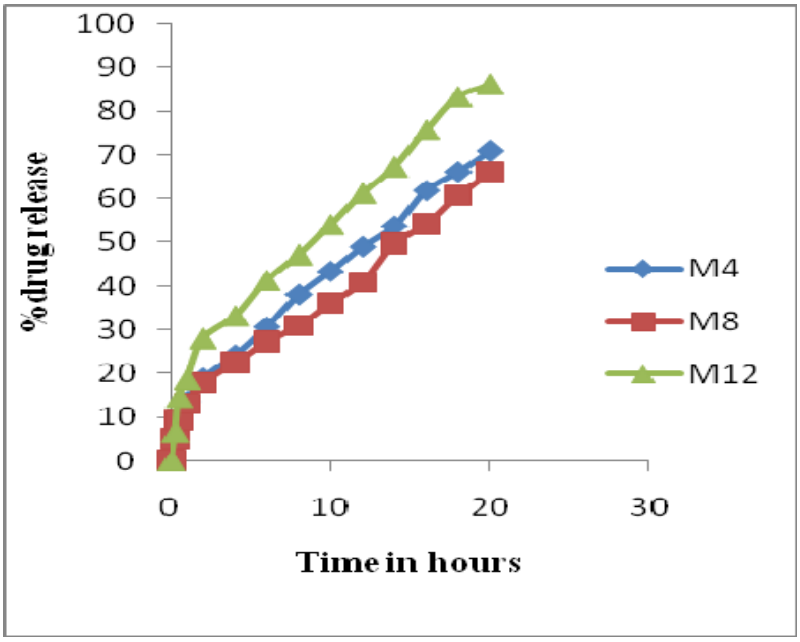
Fig : 3

***In vitro* drug release profile of Floating Duloxetine (DL) SR**



From the *in vitro* profile for **Duloxetine (DL)** SR (M4,M8&M12) the drug released was found to be 70.8%,66.19% & 86.12% respectively at the end of 20hrs. From this release profile, it was evident that the formulation M12 was suitable and it is suitable for SR formulation. (The formulation M4 &M8 did not follow the USP limit for SR i.e.,NLT 80%released at 20hrs)

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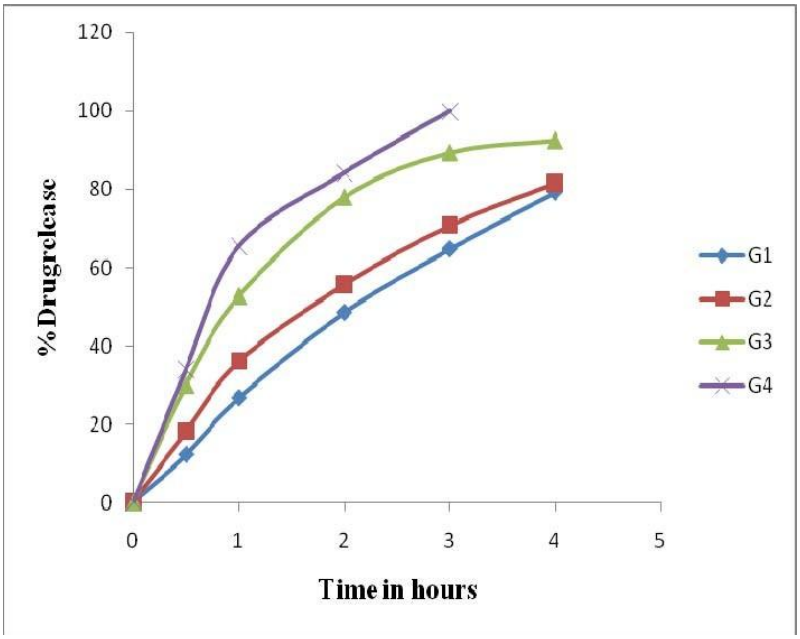
Fig : 4 *Invitro* Profile of Immediate release (G1-G4)



From the *in vitro* profile for formulation G1-G4 the drug released was found to be 64.78%, 70.83%, 89.34% & 99.95% at the end of 3 hrs. From the release profile G4 was suitable for IR formulation.

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Evaluation of Floating Bilayer tablet of Duloxetine (DL)

The results of precompression parameters for different formulation batches of Floating Bilayer tablet of **Duloxetine (DL)** tablet were shown in the table no(35).

Table no: 7

Precompression Parameters of Floating Bilayer tablet of Duloxetine (DL)

Formulation batch code	Angle of repose (°) ± S.D	Bulk density (gm) ± S.D	Tapped density (gm) ± S.D	Carr's Index (%) ± S.D	Hausner's Ratio ± S.D
C1	25.65±0.02	0.52±0.02	0.49±0.02	13.93±0.3	1.11±0.02
C2	26.93±0.3	0.54±0.04	0.54±0.34	14.92±0.5	1.19±0.1
C3	28.45±0.2	0.56±0.21	0.58±0.43	14.98±0.2	1.05±0.01
C4	24.78±0.08	0.51±0.31	0.52±0.02	12.93±0.02	1.12±0.03
C5	23.24±0.03	0.58±0.81	0.51±0.04	14.82±0.08	1.18±0.02
C6	23.67±0.34	0.49±0.09	0.59±0.03	15.92±0.72	1.12±0.2
C7	24.73±0.34	0.52±0.01	0.62±0.06	14.92±0.04	1.13±0.1
C8	23.94±0.02	0.56±0.2	0.68±0.34	13.92±0.05	1.16±0.4
C9	22.82±0.4	0.58±0.02	0.64±0.56	14.02±0.4	1.15±0.5

S.D = Standard Deviation, n=3

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Physico – Chemical Characteristics of Floating Bilayer tablet of Duloxetine (DL)

The results of physico-chemical characterization of different formulation batches of Floating Bilayer tablet were summarized in the table no (39). The results shows that the formulation C1-C9 lies within IP limits weight variation, Hardness, Friability and Drug content.

Table no:8

Physico – Chemical Characteristics of Floating Bilayer tablet of Duloxetine (DL)

Formulation batch code	Average weight of tablets(g) □ S.D	Hardness (Kg/cm^2) □ S.D	Friability (%) □ S.D	Drug content (%) □ S.D	Floating lag time (Secs)	Total buoyancy time (Hrs)
C1	0.650□ 0.23	4.4□ 0.8	0.2□ .02	97.98□ 0.25	25□ 0.2	19□ .12
C2	0.649□ 0.22	4.8□ 0.6	0.3□ 0.04	98.99□ 0.52	26□ 0.23	20□ 0.34
C3	0.651□ 0.23	4.8□ 0.82	0.2□ 0.01	99.99□ 0.9	25□ .18	20□ 0.24
C4	0.651 □ 0.14	4.2□ 0.2	0.29□ 0.06	98.26□ 0.41	28□ 0.01	21□ 0.56
C5	0.654□ 0.23	5.32□ 0.3	0.3□ 0.01	96.99□ 0.6	27□ 0.85	20□ 0.9
C6	0.650□ 0.11	5.1□ 0.5	0.2□ 0.02	99.99□ 0.12	30□ 0.12	21□ 0.2
C7	0.654□ 0.42	5.2□ 0.12	0.26□ 0.03	97.67□ 0.23	32□ 0.45	21□ 0.1
C8	0.652□ 0.2	4.4□ .12	0.24□ 0.01	98.23□ 0.45	29□ 0.38	22□ 0.8
C9	0.653□ 0.3	4.2□ .9	0.04□ 0.12	97.34□ 0.56	30□ 0.64	24□ .9

S.D = Standard Deviation, n=3

The floating lag time and total buoyancy time for formulation C3 was shown in the fig (20)

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