IJDDR International Journal of Drug Development & Research

International Journal of Drug Development & Research | January-March 2012 | Vol. 4 | Issue 1 | ISSN 0975-9344 | Available online http://www.ijddr.in
Covered in Official Product of Elsevier, The Netherlands
SJR Impact Value 0.03,& H index 2

FULL Length Research Paper
Covered in Index Copernicus with IC Value 4.68 for 2010

Formulation, Development and Evaluation of delayed release capsules of Duloxetine Hydrochloride made of different Enteric Polymers

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Abstract

Delayed release systems have acquired a centre stage in the arena of pharmaceutical research and development. The present study involves formulation and evaluation of Duloxetine Hydrochloride delayed release capsules. Duloxetine Hydrochloride is an acid labile drug. It degrades in the acidic environment of the stomach thus leading to therapeutic inefficacy. Therefore it is necessary to bypass the acidic pH of the stomach which can be achieved by formulating delayed release dosage form by using different enteric polymers. Protection of drug from acidic environment is done by coating the drug with enteric polymers by using suspension layering technique in Fluidized bed processor (FBP) with different enteric polymers like HPMCAS (Hydroxy Propyl Methyl Cellulose Acetate Succinate, Acryl EZE and HPMCP (Hydroxy propyl methyl cellulose phthalate).The formulation (E12) of delayed release capsules of Duloxetine Hydrochloride containing HPMCP (HP-55: HP-50) as enteric polymer can be taken as optimized

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***Key words*:**
Duloxetine Hydrochloride, enteric polymer

***How to Cite this Paper*:**
Pallavi Yerramsetty* , Dr. J. Vijaya Ratna, Venkata Ramana Reddy, Praveen Kumar "Formulation, Development and Evaluation of delayed release capsules of Duloxetine Hydrochloride made of different Enteric Polymers", Int. J. Drug Dev. & Res., Jan-March 2012, 4(1): 117-129

Article History:----------
Date of Submission: 18-11-2011
Date of Acceptance: 27-12-2011
Conflict of Interest: NIL
Source of Support: NONE

Introduction:

Delayed release dosage forms[1] are designed to release the drug at a time rather than promptly after administration. The delay may be time based or

based on influence of physiological conditions like GIT pH.

The drugs contained in such a system are those that are:

i) Destroyed in the stomach or by intestinal enzymes
ii) Known to cause gastric distress
iii) Absorbed from a specific intestinal site or
iv) Meant to exert local effect at a specific gastrointestinal site

Duloxetine hydrochloride is a selective serotonin norepinephrine reuptake inhibitor currently indicated for the treatment of major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, and fibromyalgia. Duloxetine Hydrochloride is an anti-depressant drug. The degradation of this anti-depressant drug in the acidic environment of stomach leads to sub therapeutic levels. In order to avoid this degradation and to bypass the acidic pH of the stomach, one of the proven approaches is formulation of delayed release dosage forms (single unit or multiple units) by using different enteric polymers in a Fluidized bed processor (FBP)[2,3,4] and the method used was solution/suspension layering. The process involves four successive coatings of Drug, Barrier material, Enteric coating material and Top coating material were given to non pareil seeds (sugar spheres)[5].

ENTERIC COATING POLYMERS

Enteric coatings are usually formulated with synthetic polymers that contain ionisable functional groups that render the polymer water soluble at a pH value.

Commonly-used enteric coatings may be made from: Methacrylic acid copolymers, Cellulose acetate (and its succinate and phthalate version), Polymethacrylic acid/acrylic acid copolymer, Hydroxypropyl methyl cellulose phthalate, Polyvinyl acetate phthalate, Hydroxyethyl ethyl cellulose phthalate, Cellulose acetate tetrahydrophtalate, Acrylic resin.

Materials:

Duloxetine Hydrochloride was from M/S Hetero Drugs Ltd, and all other chemicals and reagents used were of analytical grade.

Methods:

Preparation of Duloxetine Hydrochloride DR Capsules[6,7,8,9]:

STEPS INVOLVED IN MANUFACTURING PROCESS: (Wurster process)

1) Inert core
2) Drug Loading
3) Barrier Coating
4) Enteric Coating
5) Film Coating

1. Inert core: Sugar spheres completely dissolve in water and are available in different sizes with uniformity. So sugar spheres were selected for further development.

2. Drug loading:

Table no. 1

INGREDIENTS	D1	D2	D3	D4	D5	D6
	mg/unit					
Sugar spheres(20/25)	155.7	155.7	155.7	155.7	155.7	155.7
Duloxetine HCl	67.3	67.3	67.3	67.3	67.3	67.3
HPMC 5CPS	8.0	13.0	18.0	13.0	13.0	13.0
HPC (klucel LF)	3.0	3.0	3.0	3.0	3.0	3.0
Cross Povidone	5.0	5.0	5.0	2.0	8.0	5.0
Talc	6.0	6.0	6.0	6.0	6.0	3.0
Purified water	q.s	q.s	q.s	q.s	q.s	q.s
Total (drug layer)	245	250	255	247	250	244
% Drug coated	99.3	99.7	98.8	98.7	99.0	99.6

Binder solution was prepared by dissolving HPMC 5CPS, HPC (klucel LF) in purified water (18% w/w solution) under continuos stirring till clear solution was obtained. Duloxetine HCl was added to the above solution under continuous stirring, stirred for 15 minutes. Cross Povidone and Talc were added under

continuous stirring to the above solution, stirred to get a homogenous dispersion.

20/25 # Sugar spheres were loaded into fluid bed processor warmed for 10 minutes and

coated with the drug suspension till a weight gain of 99 % w/w, collected and were evaluated for assay.

Discussion:

Drug coating was performed on sugar spheres by using suspension layering technique[10]. The lab scale batches were developed using different binders, namely HPMC 5cps and HPC and varying binder concentrations.

- D1 formulation was planned by taking 8.0 mg of binder (HPMC 5CPS).After completion of the process more amount of fines were observed due to insufficient quantity of binder.

So further trials were planned by increasing the binder concentration.

- In D2 formulation, 13.0 mg of binder was used. No sticking was observed during the process.D2 showed 99.7% of drug loading.
- D3 formulation was planned by taking still higher binder concentration (18.0 mg).Sticking was observed during the process and the % yield was less.

Further trials D4, D5, D6 were planned by varying the amount of disintegrant. D2 formulation containing 13.0 mg of binder and 5 mg of disintegrant showed 99.7% of drug loading. Hence this formulation was chosen as the optimized formulation to be taken up for further coating stages

3. BARRIER COATING:

Main aim of barrier coating is to protect the drug coated pellets from reacting with the enteric coating and environmental conditions.

PREPARATION OF BARRIER COATING SUSPENSION:

HPMC 5CPS was added to purified water (10%w/w) under continuous stirring. Tri ethyl citrate was added to the above solution under stirring. Titanium dioxide and talc (sifted through 100 mesh) were added to the above solution, stirred to get a homogenous dispersion.

Drug loaded pellets (D2) were loaded into FBP, pellets were warmed till the product temperature of 30-35˚C was obtained. The sub coating dispersion was sprayed till target weight build up was obtained.

Table no. 2

INGREDIENTS	B1	B2	B3	B4	B5
	mg/unit				
Drug loaded pellets (D2)	250	250	250	250	250
HPMC 5CPS	6.0	6.0	6.0	8.0	12.0
Sucrose	4.0	8.0	-	-	-
Tri ethyl citrate	1.25	1.25	1.25	1.25	1.25
Titanium dioxide	2.7	2.7	2.7	2.7	2.7
Talc	0.5	0.5	0.5	0.5	0.5
Purified water	q.s	q.s	q.s	q.s	q.s
Total	264.5	268.5	260.5	262.5	266.5

Dissolution in direct 6.8 phosphate buffer (Table no. 3)

Time(min)	B1	B2	B3	B4	B5
	% Drug dissolved				
15	96	97	96	95	83
30	99	100	99	99	92
45	100	100	100	100	98
60	99	99	100	100	100
90	99	99	100	90	99

Optimization of Barrier Coatings

- In Barrier coating, HPMC 5CPS is used as binder. B1, B2 formulations were planned by using sucrose as release modifier. Due to incorporation of sucrose, thickening of suspension was observed and there is no effect on dissolution. So sucrose to be removed for further trials.
- In B3 only HPMC 5 CPS was used. Fines were observed after completion of the process. So further trials were planned by increasing the binder concentration.
- B4, B5 were planned by using 8 mg, 12 mg of HPMC 5 CPS. In case of B5, the dissolution profile is

poor and thickening of suspension is observed.

- So, B4 formulation was optimized for barrier coating.

4. ENTERIC COATING:

Enteric coating was given to barrier coated pellets. Trials were taken using different enteric polymers.

Selection of enteric polymer (Table no. 4)

INGREDIENTS	E1	E2	E3	E4
	mg/unit			
Barrier coated pellets(B4)	262.5	262.5	**262.5**	262.5
Acryl EZE	-	54	**-**	**-**
HPMC Phthalate (HP 55)	-	-	**54**	-
HPMC Phthalate (HP 55 S)	-	-	**-**	54
HPMC Acetate succinate	54	-	**-**	-
Tri ethyl citrate	6	6	**6**	6
Talc	5	5	**5**	5
Purified water	q.s	q.s	**-**	-
IPA/DCM (1:1)	-	-	**q.s**	q.s
Total	327.5	327.5	**327.5**	327.5

Dissolution in 0.1 N HCl followed by 6.8 phosphate buffer (Table no. 5)

Time(min)	E1	E2	E3	E4
	% Drug dissolved			
15	42	35	43	32
30	69	77	75	65
45	81	86	83	76
60	87	90	90	84
90	95	95	96	91

Dissolution in 0.1 N HCl followed by 5.5 phosphate buffer (Table no. 6)

Time(min)	E1	E2	E3	E4
	% Drug dissolved			
15	1	0	1	0
30	18	0	21	1
45	43	1	48	6
60	65	3	62	28
90	84	5	85	53

Selection of enteric polymer: **(Table no. 7)**

S. No	Formulation	Enteric polymer
1.	E1	HPMC Acetate succinate
2.	E2	Acryl EZE
3.	E3	HPMC Phthalate (HP 55)
4.	E4	HPMC Phthalate (HP 55 S)

Discussion:

- HPMC Acetate succinate (HPMCAS) was used as enteric polymer in E1. HPMCAS is a costly material. Innovator also used the same polymer. So further trials were planned by using different polymers.
- In E2, Acryl EZE was used as enteric polymer. E2 showed only 5% drug release in pH 5.5 phosphate buffer even after 90 min. So further trials were planned.
- HPMC Phthalate (HP 55) and HPMC Phthalate (HP 55S) were used in E3 and E4 respectively.
- The enteric coating suspension was very viscous in case of E4 and the process was very slow. Formation of multiples was also observed. So HPMC Phthalate (HP 55) was selected as enteric polymer.

Table no. 8

Ingredients	E5	E6	E7	E8	E9
	mg/unit				
Barrier coated pellets(B4)	262.5	262.5	262.5	262.5	262.5
HPMC Phthalate (HP 55)	54	-	32.4	27	21.6
HPMC Phthalate (HP 50)	-	54	21.6	27	32.4
Tri ethyl citrate	6	6	6	6	6
Talc	5	5	5	5	5
Acetone: water(8:2)	q.s	q.s	q.s	q.s	q.s
Total enteric layer	327.5	327.5	327.5	327.5	327.5

Dissolution in 0.1 N HCl followed by pH 6.8 phosphate buffer (Table no. 9)

Time(min)	E5	E6	E7	E8	E9
	% Drug dissolved				
15	42	45	43	46	44
30	76	81	78	80	79
45	84	87	86	87	90
60	90	93	92	90	92
90	93	97	96	92	96

Dissolution in 0.1 N HCl followed by pH 5.5 phosphate buffer (Table no. 10)

Time(min)	E5	E6	E7	E8	E9
	% Drug dissolved				
15	1	6	2	4	5
30	3	35	20	26	1
45	21	56	56	55	54
60	32	71	74	69	70
90	45	89	86	83	84

Discussion:

- HPMC Phthalate (HP 55) was used in E5. The drug release in pH 5.5 phosphate buffer was poor. When HPMC Phthalate (HP 50) was used in E6, the drug release pattern was high when compared to innovator. So a combination of HPMC Phthalate (HP 55) and HPMC Phthalate (HP 50) were used in E7 in 6:4 ratio.
- E7 formulation was optimized for enteric coating.
- In E8, a combination of HPMC Phthalate (HP 55) and HPMC Phthalate (HP 50) were used in 5:5 ratio. In E9, a combination of HPMC Phthalate (HP 55) and HPMC Phthalate (HP 50) were used in 6:4 ratio. The dissolution profile did not match with the innovator. So E7 formulation was optimized**.**

SOLVENT SELECTION (Table no. 11)

Ingredients	E10	E11	E12
	mg/unit		
HPMC Phthalate (HP 55)	32.4	32.4	**32.4**
HPMC Phthalate (HP 50)	21.6	21.6	**21.6**
Tri ethyl citrate	6	6	**6**
Talc	5	5	**5**
IPA/DCM(1:1)	1:1	-	**-**
Acetone/Water	-	1:1	**8:2**
Total	327.5	327.5	**327.5**

Dissolution in 0.1 N HCl followed by pH 6.8 phosphate buffer (Table no. 12)

Time(min)	E10	E11	E12
	% Drug dissolved		
15	39	-	45
30	70	-	75
45	85	-	86
60	91	-	91
90	95	-	95
120	97	-	99

Dissolution in 0.1 N HCl followed by pH 5.5 phosphate buffer (Table no. 13)

Time(min)	E10	E11	E12
	% Drug dissolved		
15	1	2	0
30	16	20	21
45	51	56	65
60	70	74	81
90	83	86	91

Discussion:

- IPA/DCM were used in 1:1 ratio as solvents in E10 formulation. Even though invitro drug release is good, as DCM is class III solvent, it is to be avoided in the formulation. So class II solvents to be used for further trials.
- In E11, Acetone/water 1:1 ratio was used as solvent system. This solvent system was not suitable for HPMCP as clear solution was not obtained. So more acetone and less water to be used for further trials.
- Acetone/water 8:2 ratio was used as solvent system in E12 formulation. The dissolution profile matched with that of innovator.

Preparation of enteric coating suspension:

Acetone and water were taken in 8:2 ratio in a stainless steel vessel. HPMCP (HP-55), HPMCP (HP-50), were slowly added to this solvent, under stirring and the contents were mixed for 15 minutes under continuous stirring. TEC, Talc were added to the above solution, under continuous stirring, stirred till a homogenous dispersion was formed. The dispersion of the above step was sifted through mesh # 100 and collected in a stainless steel vessel.

The sub coated pellets were loaded into FBP, warmed till product temperature of 28˚C-35˚C was obtained. The enteric coating dispersion was sprayed with the following parameters. Coating was continued till target build up was obtained.

5. TOP COATING

Table no. 14

Ingredients	F1 mg/unit
Opadry Y-1-7000 White*	**7.2**
Talc	**7.2**
Purified water	**q.s**

* - Approved ready mix for film coating, this comprises hypromellose, polyethylene glycol, titanium dioxide

Top coating[11] was given to improve the elegance and mechanical resistance of the pellets.

Dissolution in 0.1 N HCl followed by pH 6.8 phosphate buffer (Table no. 15)

Time(min)	F1 % Drug dissolved
15	44
30	74
45	86
60	91
90	96
120	99

OPTIMIZED FORMULATION (Table no. 16)

S. No.	INGREDIENTS	mg/unit
I	**DRUG LOADING (D2)**	
1	Sugar spheres (20/25)	155.7
2	Duloxetine hydrochloride	67.3
3	Hypromellose 5cps	13
4	HPC (klucel LF)	3
5	Crospovidone	5
6	Talc	6
7	Purified water	q.s
	Total	**250**
II	**SUB COATING (B4)**	
8	Drug coated pellets	250
9	Hydroxy propyl methyl cellulose 5CPS	8
10	Triethyl citrate	1.25
11	Titanium dioxide	2.7
12	Talc	0.5
13	Purified water	q.s
	Total	**262.5**
III	**ENTERIC COATING (E12)**	
14	Sub coated pellets	262.5
15	HPMC phthalate (HP55)	32.4
16	HPMC phthalate (HP50)	21.6
17	Triethyl citrate	6.75
18	Talc	5.25
19	Acetone/ water	8:2
	Total	**327.5**
IV	**TOP COATING (F1)**	
20	Enteric coated pellets	**327.5**
21	Opadry-Y-1-7000 White	7.2
22	Talc	7.2
23	Purified water	q.s
	Total	**342**

EVALUATION OF DELAYED RELEASE FORMULATIONS AND COMPARISION WITH INNOVATOR

Delayed release formulation was evaluated for

- Assay
- Acid resistance
- Drug Release
- Dissolution (acid stage followed by buffer stage)
- Kinetic studies of Innovator and Optimized formulation
- Stability studies of Optimized formulation

RESULTS AND DISCUSSION

Optimization of enteric coating was done by comparing the parameters like assay, acid resistance and dissolution of the EC pellets with the innovator.

Assay

The enteric coated pellets prepared complied with the in-house specifications of assay results.

Acid resistance

Acid resistance was conducted by HPLC technique to check the acid resistance of Duloxetine Hydrochloride enteric coated capsules.The enteric coated pellets prepared complied with the in-house specifications of Acid resistance results.

Table no. 17

S. No	Batch No	Assay (specifications: 98 – 102)	Acid resistance (specifications: 98 – 102)
1.	**Innovator**	**101%**	**99%**
2.	E1	100%	97.6%
3.	E2	99.7%	99.7%
4.	E3	99.8%	99.4%
5.	E4	98.6%	98%
6.	E5	99.4%	98.4%
7.	E6	99.6%	99.2%
8.	E7	100%	98.2%
9.	E8	99.7%	98.6%
10.	E9	99.8%	97.5%
11.	E10	98.6%	98.2%
12.	E11	99.4%	99.2%
13.	E12	99.6%	99.4%

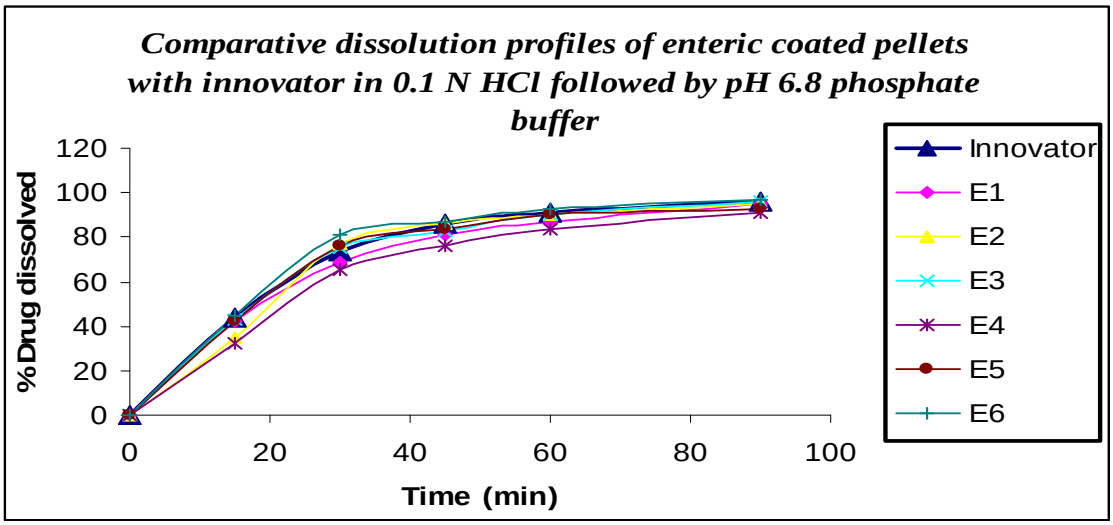
DISSOLUTION

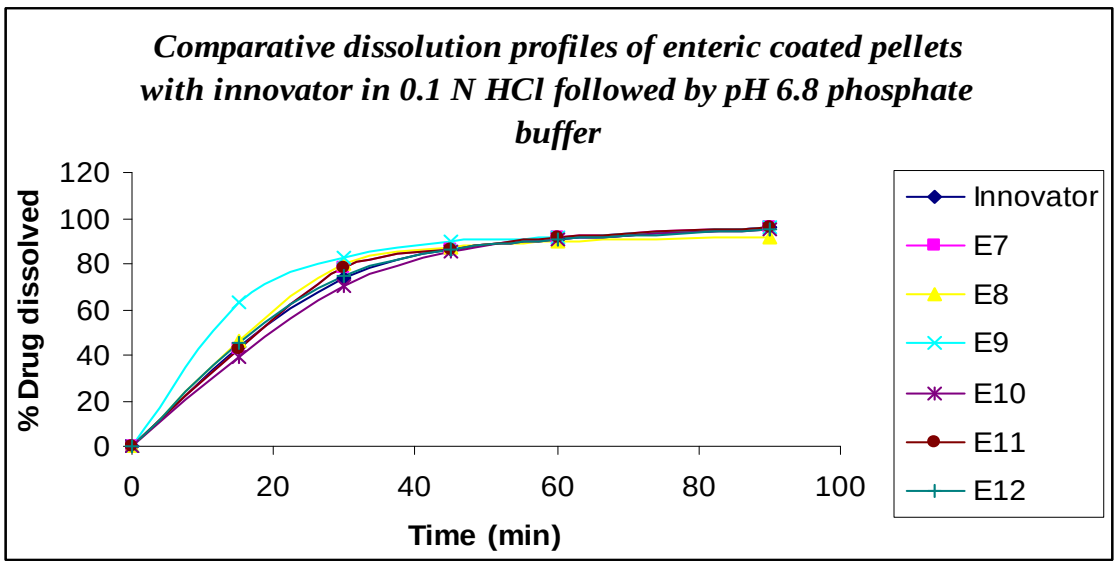
Acid stage: 0.1 N HCl, 1000ml, paddle, 100rpm, 120 minutes.

Buffer stage: pH 6.8 phosphate buffer, 1000ml, paddle, 100rpm, Sampling points 15, 30, 45, 60 and 90 minutes

Dissolution profile of enteric coated pellets in 0.1N HCl followed by 6.8 Phosphate buffer (Table no. 18)

Time (min)	Innovator	E1	E2	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12
	(% labelled amount dissolved in buffer)												
15	**44**	42	35	43	32	42	45	43	46	63	39	43	45
30	**74**	69	77	75	65	76	81	78	80	83	70	78	75
45	**86**	81	86	83	76	84	87	86	87	90	85	86	86
60	**91**	87	90	90	84	90	93	92	90	92	91	92	91
90	**96**	95	95	96	91	93	97	96	92	96	95	96	95



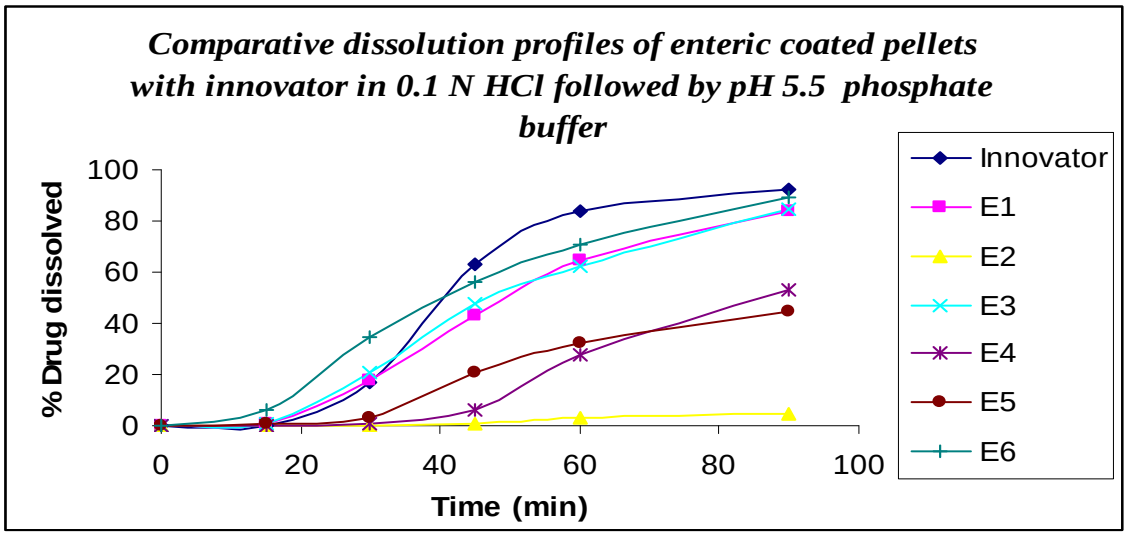


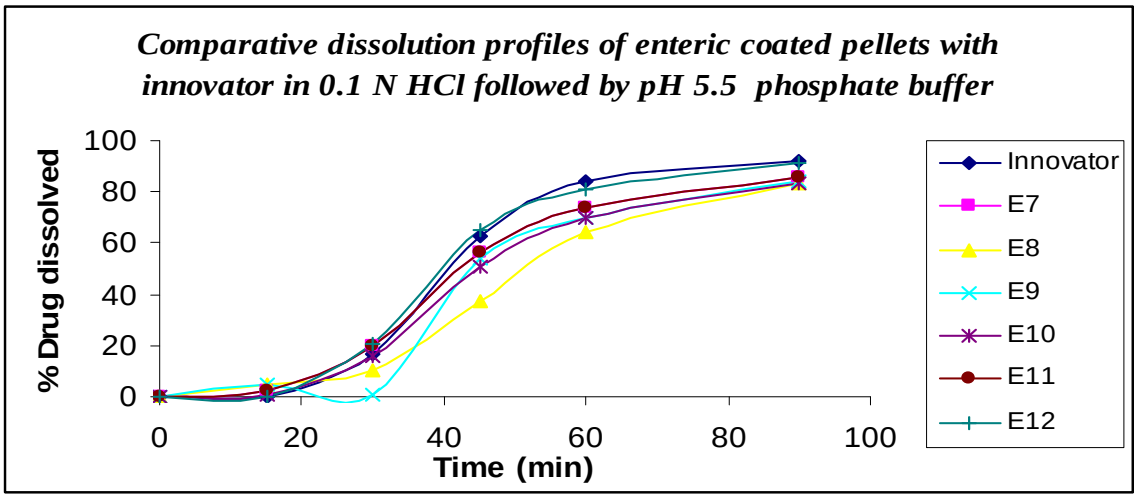
From the comparative dissolution profile with the innovator it is evident that all the enteric polymers show similar drug release pattern in the official media.
So the dissolution profile was observed in the discriminating media (pH 5.5 phosphate buffer).

Dissolution profile of enteric coated pellets in 0.1N HCl followed by 5.5 Phosphate buffer (Table no. 19)

Time (min)	Innovator	E1	E2	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12
	(% labelled amount dissolved in buffer)												
15	**0**	1	0	1	0	1	6	2	5	5	1	2	0
30	**17**	18	0	21	1	3	35	20	10	1	16	20	21
45	**63**	43	1	48	6	21	56	56	37	54	51	56	65
60	**84**	65	3	62	28	32	71	74	64	70	70	74	81
90	**92**	84	5	85	53	45	89	86	83	84	83	86	91

Dissolution profile of enteric coated pellets in 0.1N HCl followed by 5.5 Phosphate buffer





From the above comparative dissolution profile, it is evident that the drug release pattern of formulation E12 matched with that of the innovator.

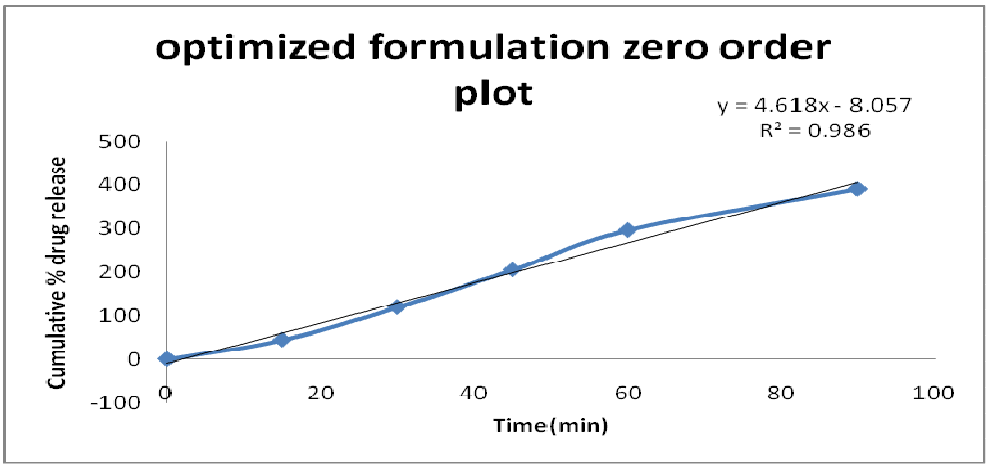
Release kinetics

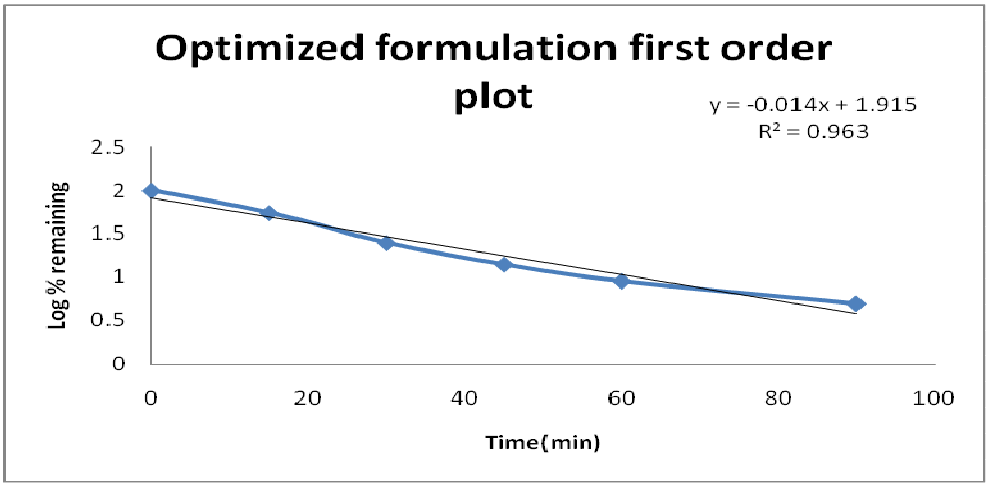
Different kinetic models were applied to optimized enteric coated formula and the results are shown in Table

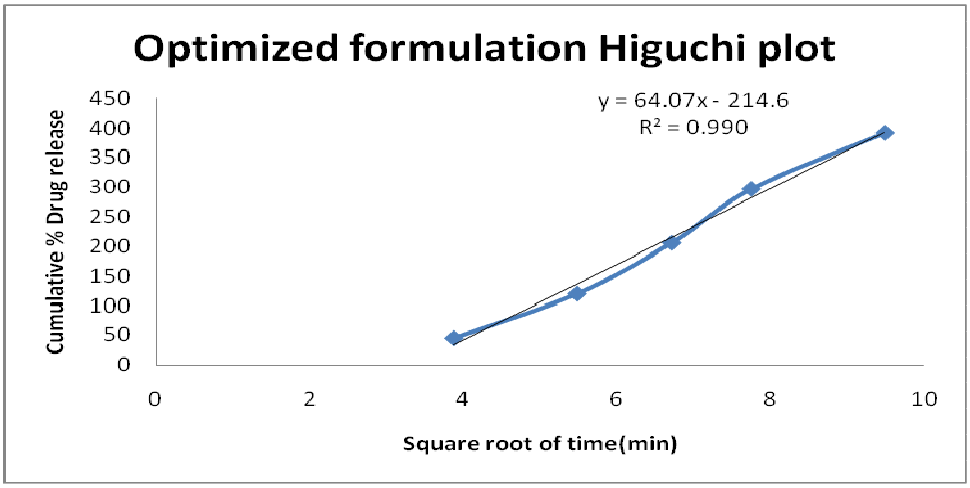
Table no. 20

Kinetics	Zero order	First order	Higuchi
	r²	r²	r²
Innovator	0.987	0.982	0.990
Optimized formulation (E12)	0.986	0.963	0.990

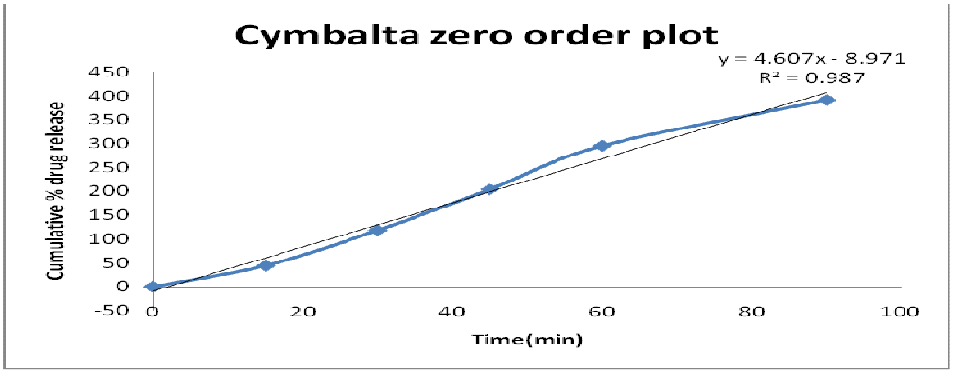
Kinetic models for optimized formulation

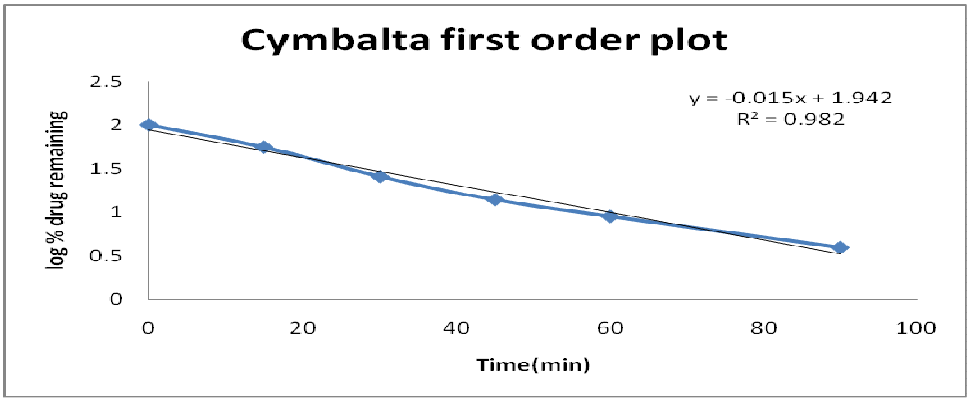


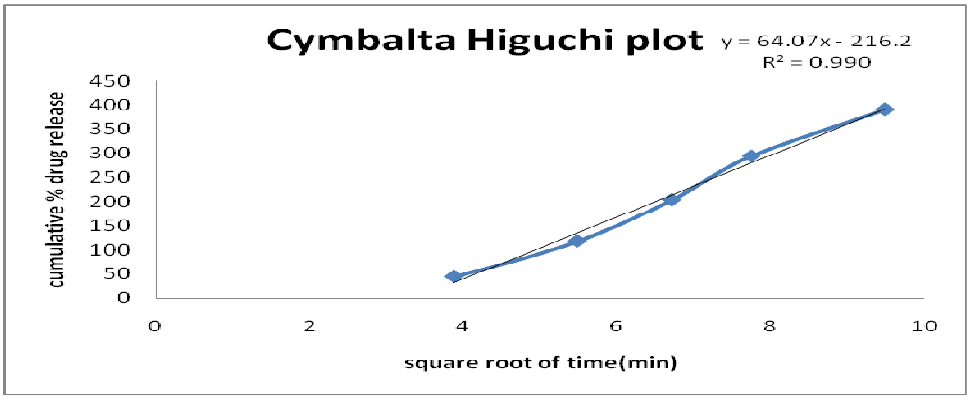




Kinetics models for innovator







Study of similarity (f_2) factors

Calculation of similarity factor (f_2)

Similarity factor (f_2)

Similarity factor (f_2) was calculated to compare the test with reference release profiles. It was calculated from the mean dissolution data according to the following equation.

$$f_2 = 50 \log \left\{ [1 + (1/n)\sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100 \right\}$$

Where , n – No. of full points
R_t – The reference profile at the time point t
T_t – The test profile at the same point.

Table no. 21

Time (min)	Cumulative % drug release	
	Innovator	E12
15	44	45
30	74	75
45	86	86
60	91	91
90	96	95
F_2 value	**-**	**93.0**

Discussion:

Value of similarity factor (f_2) of E12 with innovator was found to be 93.0 and indicated that in-vitro release of E12 was similar with the Marketed sample

Differential Scanning Calorimetry (DSC)

DSC is very useful in the investigation of the thermal properties of pellets, providing both qualitative and quantitative information about the physicochemical state of drug inside the pellets. There was no detectable endotherm if the drug is present in a molecular dispersion or solid solution state in the polymeric pellets loaded with drug. In the present investigation, DSC thermograms of pure drug, drug and polymer physical mixtures as shown in Figure 1 to Figure 3, prominent melting endotherms of pure drug and a physical mixture of drug and polymer were found at 171.7°C and 175.1°C. Drug-loaded Pellets showed a broad small peak at 171.5°C, indicating the presence of drug in crystalline form. The reduction of height and sharpness of the endotherm peak is due to the presence of polymers in the Pellets.

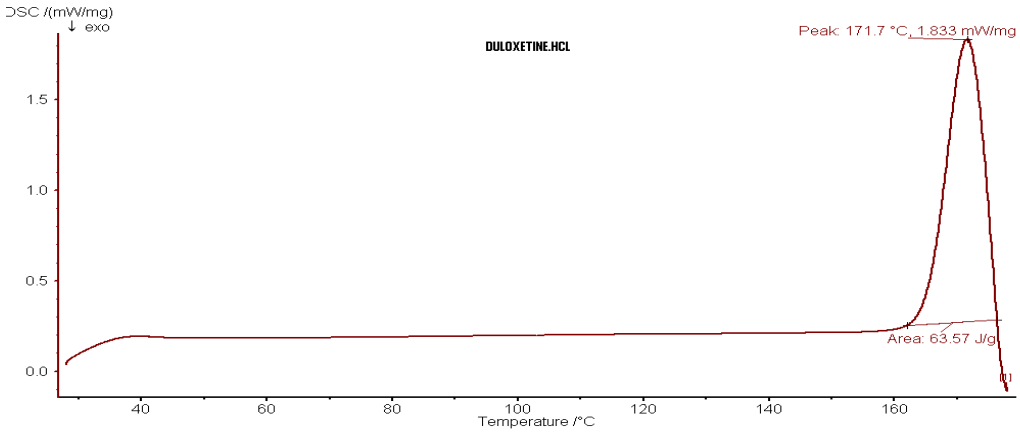


Figure 1-DSC Thermogram of Duloxetine HCL

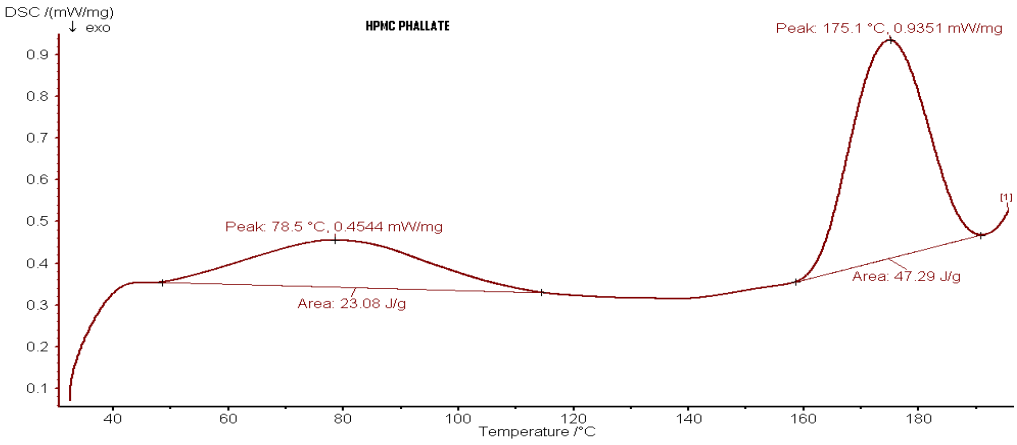


Figure 2-DSC Thermogram of HPMC Phthalate

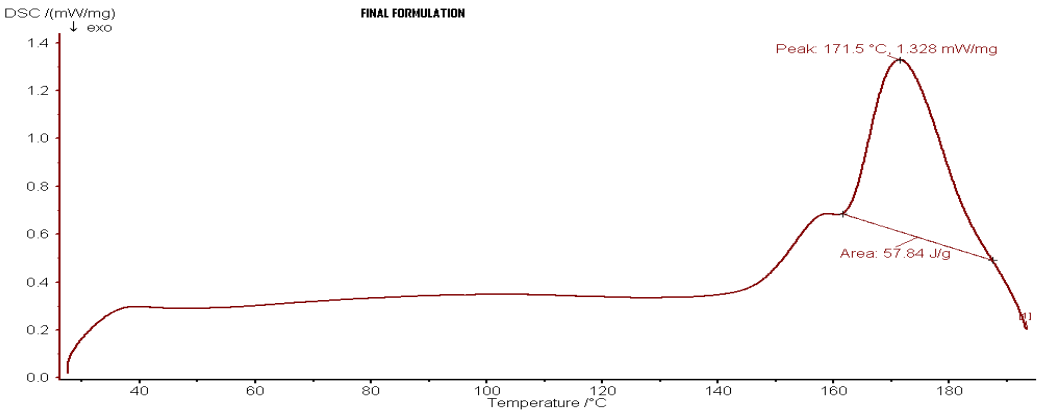


Figure 3-DSC Thermogram of Final Formulation

Conclusion:

The present study was to formulate and evaluate delayed release capsules of Duloxetine Hydrochloride.

The formulation process was carried out in FBP by suspension layering technique.

Duloxetine Hydrochloride is an acid labile drug, degrades at acidic pH of stomach. To bypass stomach, the formulation has to delay the release and give the release in proximal small intestine. This can be achieved by enteric coating.

The work was carried out to delay the release of Duloxetine Hydrochloride by using enteric polymer. The study includes formulation and evaluation, release kinetics and stability studies of capsules.

The inert core material (i.e. sugar spheres 20/25#) was given Drug coating, Barrier coating, Enteric coating and Top coating.

Drug coating was given to sugar spheres by using different binders i.e., HPMC 5cps and HPC (klucel LF) with different concentrations..

Barrier coating was given to drug loaded pellets to avoid direct contact with enteric coating. Barrier coating was given with HPMC 5cps and TEC combination at an average weight build up of barrier coated pellets.

Enteric coating was given to Duloxetine Hydrochloride pellets by HPMCP (HP-55: HP-50 6:4). Enteric coating was optimized at an average weight build up and release profile was compared with Innovator. Enteric coated pellets were evaluated for assay, acid resistance and dissolution; E12 enteric coated pellets were found to be optimized and were evaluated and the results were found to be more similar with innovator.

Different kinetic models were applied to optimized enteric coated formulation (E12) and observed that it follows zero order kinetics with Higuchi diffusion mechanism.

Stability studies were conducted at 40°C / 75% RH (accelerated stability testing) for 2 months. Assay, acid resistance, dissolution release profile of optimized enteric coated formulation (E12) complies with Innovator and was found to be stable.

Based on the above data, it was concluded that Duloxetine Hydrochloride Capsules 60mg (E12) complies with the Innovator and may be considered as an ideal formulation for developing Duloxetine Hydrochloride delayed release capsules 60mg.

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