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DULOXETINE HYDROCHLORIDE DELAYED RELEASE PELLETS PREPARED BY SUSPENSION LAYER METHOD

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ABSTRACT

The aim of present study is to develop a delayed release pellets dosage form of duloxetine hydrochloride with a suitable polymer by using suspension layered method. Drug loaded nuclei was prepared using suspension layered technique in a Fluidized Bed Processor, the nuclei was coated with an acid resistant acrylic polymer (Eudragit L30-D55) and compared acid resistant properties with HPMC phthalate. The entire coating process performed in a Fluidized Bed Processor to different thickness. The *in vitro* dissolution studies were conducted in 0.1N HCl for 2 hours followed by phosphate buffer (pH 6.8) for 1 hour with USP dissolution tester (type II). The results generated in this study showed that proper selection of polymer material based on their physicochemical properties as well as polymer load is important in designing delayed release pellets dosage form with best fit of dissolution profile.

INTRODUCTION: Delayed release dosages [1] form is designed to provide spatial placement or temporal targeted delivery of a drug to the distal human gut. Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery reports desired rate of drug release to targeted tissue over a specified period of treatment.

The primary aim of using delayed-release product is to protect the drug from gastric fluids, to reduce gastric distress caused by drug particularly irritating to the stomach**,** and to avoid toxic complex formation or to facilitate gastro intestinal transit for drugs that are better absorbed from intestine.

Delayed release products are typically enteric-coated or targeted to the colon. The oral route of drug delivery is typically considered the preferred and most patient convenient drug administration. The release of drug from an oral dosage form maybe intentionally delayed until it reaches the intestine.

Duloxetine HCl drug causes gastric irritation to intestinal mucosa and it forms unwanted toxic product of naphthol when reacted with 0.1n HCl. Duloxetine HCl shows good absorption at intestinal ph. Ideal polymer is required to prevent drug leaching from pellets in the acidic medium and releases drug at basic medium

MATERIALS AND METHODS [2, 3]**:** Duloxetine Hydro-chloride, spheres 25/30was obtained from S.D. fine chemicals, Pvt. Ltd. Povidone k29/30 obtained from Himedia Laboratories Pvt. Ltd, Mumbai.

Hydroxy propyl cellulose obtained from Loba Chemie Pvt Ltd, Mumbai. Eudragit L30-D55 was obtained from S.D fine chemicals, pvt.ltd. All other ingredients are of laboratory grade.

Formulation of Duloxetine Hydrochloride Pellets:

TABLE 1: FORMULATION OF DULOXETINE HYDROCHLORIDE PELLETS

S. NO	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
	DRUG COATING								
1.	Duloxetine HCl*	67.3	67.3	67.3	67.3	67.3	67.3	67.3	67.3
2.	Sugar spheres 25/30	143.2	143.2	143.2	143.2	143.2	143.2	143.2	143.2
3.	Povidone K29/32	31.4	26.4	31.4	26.4	27.4	22.4	27.4	22.4
4.	HPC (SSL)	3	3	3	3	3	3	3	3
5.	Talc	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
6.	Cross Povidone	-	5	-	5	-	5	-	5
7.	Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	BARRIER COATING								
8.	HPMC 5 CPS	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
9.	Sucrose	7	7	7	7	7	7	7	7
10.	Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
11	Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	ENTERIC COATING								
12	Eudragit L30-D55	-	-	60	60	-	-	60	60
13	Sodium hydroxide	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
14	Triethylcitrate	4	4	4	4	8	8	8	8
15	Talc	6	6	6	6	6	6	6	6
16	Povidone K29/32	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
17	HPMC phthalate (HP55)	60	60	-	-	60	60	-	-

*67.3 mg Duloxetine hydrochloride contains the 60 mg of active Duloxetine

- **Manufacturing Process [3, 4, 5]:** In suspension layered method pellets were prepared by 3 sequential coatings
    - Drug coating:
    - Barrier coating:
    - Enteric coating:
- **Drug Coating:**
    - **Preparation of drug suspension:**
    - Duloxetine HCl & HPC added to 240gms of water under continuous stirring (step 1)
    - Cross povidone &talc were dispersed in 408gms of purified water using lab stirrer (step 2)
    - Step1 preparation kept for stirring to this added step 2 preparation & stirred for 30 minutes. This preparation is called primary suspension
    - Sugar spheres #20/25 were loaded in to F.B.P warmed for 10 minutes, sugar spheres were coated with primary suspension
    - Drug loaded pellets were collected (step 3)
- **Barrier Coating:**
    - **Preparation of barrier suspension:**
        - HPMC, Talc, Sucrose were added under continuous stirring to prepare barrier suspension
- **Coating of barrier suspension:**
    - Step 3 pellets were loaded in to F.B.P. & coated with above prepared barrier suspension.

Enteric Coating:

- **Hydroxy propyl methyl cellulose pthalate Enteric Coating preparation [8, 9]**: HPMCP was slowly added to IPA & dichloro methane (1:1) in a stain less steel vessel to this solution triethyl citrate, talc was added. This is the HPMCp enteric coating solution
- **Eudragit L 30-D55 Enteric Coating Preparation:** Eudragit L30-D55 was slowly added to the purified water along with the NAOH under continuous stirring. Triethyl citrate, povidone k29/32were dissolved in the purified water this prepared solution added to above preparation.

The finally prepared solution called Eudragit L30-D55 enteric coating solution.

- **Coating of enteric suspension:** The barrier suspension coated pellets were loaded in to F.B.P and pellets were warmed till product temperature 28˚C-35˚C.the enteric coating suspension was sprayed.

Evaluation of Formulated Duloxetine Hydrochloride Pellets:

Physical evaluation of Pellets:

Friability test to Pellets [5]: Friability of pellets was tested with friabilator at 25 rpm for 25 minutes along with glass spheres of 5µm diameter. Moisture content of coated pellets was determined by loss on drying of the pellets under vacuum at 60˚C for 4 hours. Bulk density of coated pellets was measured by using 100ml conical flask.

Assay:

1. **Assay procedure of Standard Solution:** Weigh 68mg of Duloxetine HCl and transfer into 100ml volumetric flask. The contents were ultra sonicated for 15min with 20ml of HPLC methanol and made up to the mark with same. The resulting solution was allowed to settle for about an hour. Transfer 5.0 ml of the above solution into a 50ml volumetric flask; dilute it with diluents and mix thoroughly to calculate the percentage purity of drug.

2. **Assay procedure of Test preparation:** Twenty capsule contents were weighed accurately. The average weight was determined and then ground to a fine powder. A quantity equivalent to 20mg was transferred to a 100ml volumetric flask. The contents were ultra sonicated for 15min with 50ml of HPLC methanol and made up to the mark with same. The resulting solution was allowed to settle for about an hour. The solution was filtered using 0.45µm membrane filter. The drug content per capsule (on an average weight basis) was calculated.

$$\%Assay = \frac{\text{Sample area x Std. wt. x Avg. wt. x std. purity x dilution factor}}{\text{Std. area x Sample wt. x 100}}$$

Acid Resistance: Enteric protection from delayed release film coating system has been influenced by the hydrophilic & lipophilic properties of the plasticizer, level of plasticizer & amount of polymer applied to the substrate. The purpose of this study was to evaluate the influence of the coating material prepared by included plasticizer in coating material. The pellets were tested in 2 different media, 0.1N HCl and 0.5M sodium acetate buffer (pH 4.5) to simulate the stomach pH of a fasted human.

Acid uptake testing was performed in a Vankel 35-1200 disintegration apparatus. The disintegration time of the uncoated pellets in 900ml of (0.1N HCl), and acetate buffer (pH 4.5) were recorded. The test repeated with the coated pellets. The amount of media taken up by the coated and uncoated pellet was determined by calculating the percent difference between pellet weight before and after exposure to media for 2 hrs.

***In vitro* Dissolution Studies of Pellets: [6]**

Method: Dissolution studies were carried out for all the formulations combinations in triplicate, employing USP-II basket method and 900ml of 0.1N HCl, pH-6.8 as the dissolution medium. The medium was allowed to equilibrate to temp of 37°C±0.5°C. Pellets were placed in the vessel and the vessel was covered the apparatus was operated for 2 hrs in 0.1 N HCl and next 1.5 hrs pH-6.8 phosphate buffer at 100 rpm. At definite time intervals of 5 ml of the aliquot of sample was with drawn periodically and the volume replaced with equivalent amount of the fresh dissolution medium. The samples were analyzed spectrophotometrically at 288 nm using UV-spectrophotometer

RESULTS AND DISCUSSION:

TABLE 2: ASSAY STUDIES

S. NO	FORMULATIONS	% ASSAY
1	F1	100±0.8
2	F2	99.8±0.5
3	F3	99.7±0.1
4	F4	101±0.8
5	F5	99.8±0.2
6	F6	99.6±0.1
7	F7	100.2±0.2
8	F8	100.4±0.1

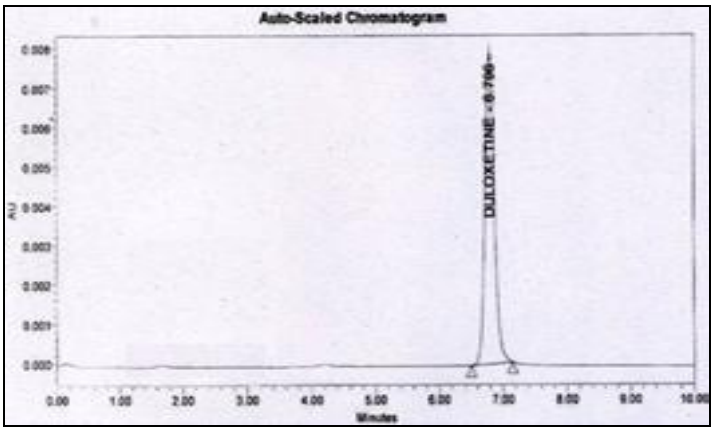

FIG. 1a

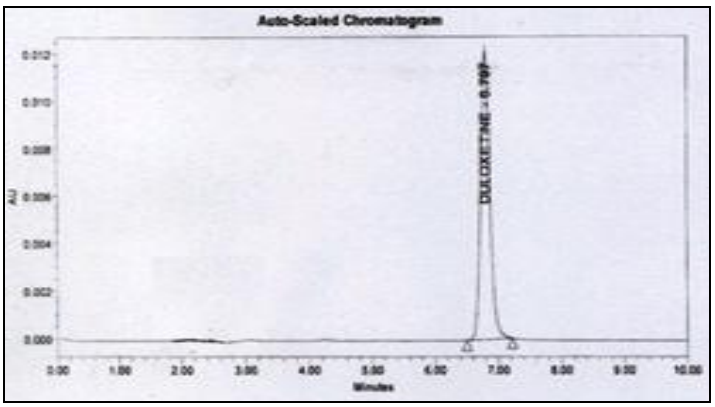

FIG. 1b

FIG. 1: CHROMATOGRAM OF DULOXETINE HYDROCHLORIDE PURE DRUG& PHYSICAL MIXTURE

HPLC peak showing a retention time of 6.796

Evaluation of Formulated Pellets [7]:

Acid Resistance: Dissolution study of Duloxetine HCL was carried out using 0.1N HCl. There was slow release in the acidic medium. The studies were conducted for F1 to F8 formulations. In that F8 batch was shown 0.8% ± 0.002% of drug release in 120 minutes compared to other formulations. It was observed that the formulations showed delayed drug release. In F8 batch Eudragit L30-D55 polymer was used, this is also one reason for obtaining the better result of F8 batch.

% Acid release= % Assay - % of Assay after acid treatment (Acid resistance)

TABLE 3: ACID RESISTANCE

FORMULATIONS	% ACID RESISTANCE
F1	98.4±0.12
F2	98.1±0.08
F3	98.4±0.04
F4	97.9±0.06
F5	98.2±0.10
F6	98.5±0.09
F7	98.9±0.07
F8	99.6±0.11

In acid resistance test f8 formulation has given the ideal value 99.6

***In vitro* Studies:**

Acid Stage: 0.1N HCl, 1000ml, Basket, 100rpm, 2hrs

Sampling points: 30, 60, 120mins

pH 6.8 stage: 1000ml, Basket, 100rpm, Sampling points: 130, 150, 165, 180, 210 mins

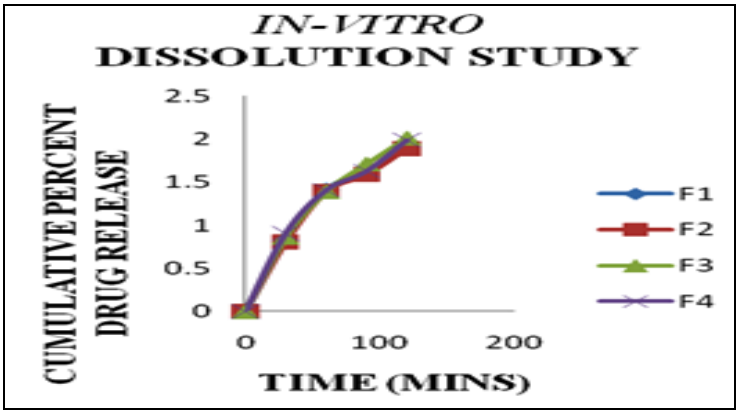

FIG. 2a

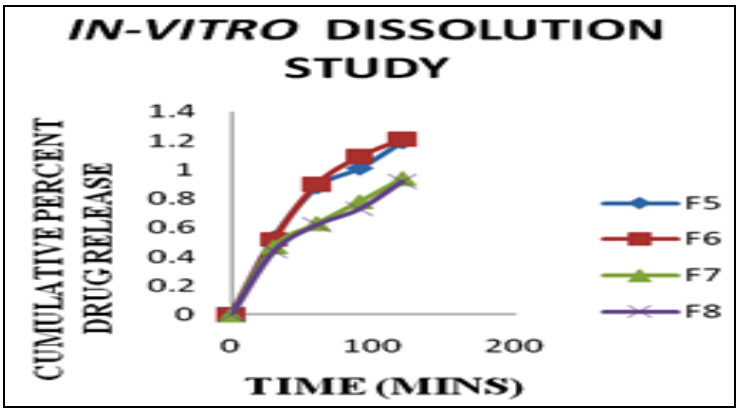

FIG. 2b

FIG. 2: CUMULATIVE PERCENTAGE OF RELEASE OF DULOXETINE HCL IN 0.1N HCl

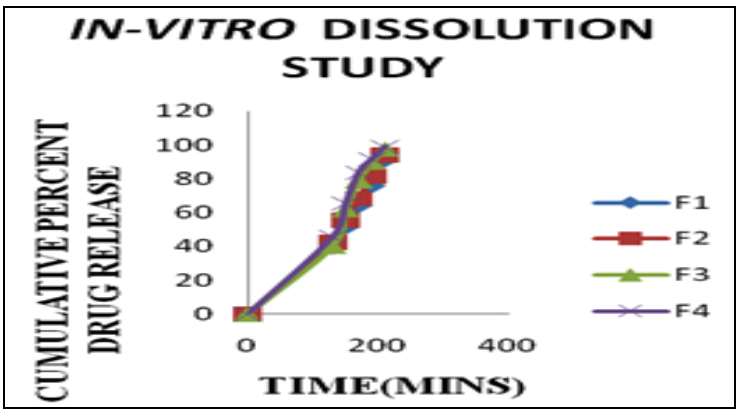

FIG. **3a**

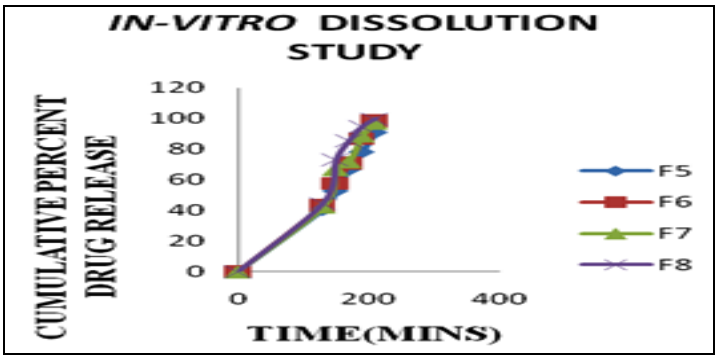

FIG. 3b

FIG. 3: CUMULATIVE PERCENTAGE OF DULOXETINE HCl IN PHOSPHATE BUFFER MEDIUM (pH 6.8)

CONCLUSION: Pellets were prepared by using Suspension Layered Method. Finished products were evaluated for Assay studies and *in-vitro* drug release studies. The developed trials were tested for *In-vitro* dissolution studies performed for 2hr in acidic media at 0.1N HCl. After that, 1.50 minutes in 6.8 ph Phosphate buffer. From the results and discussion, it may be concluded that the F8 formulation is an optimized formulation from F1 to F8. In 3.5 hour's release, it fulfills all the requirements of enteric coated pellets and performed long term stability study on this formulation.

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