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Formulation and Evaluation of Duloxetine Hydrochloride Sustained Release Pellets

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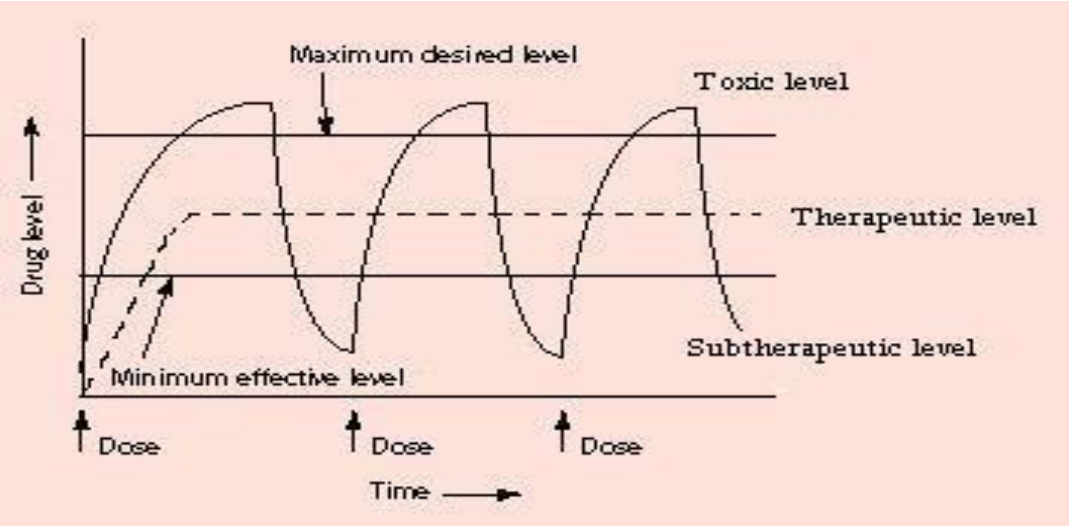
ABSTRACT

The main aim of the work is to Investigated to develop Duloxetine hydrochloride-layered tablets for obtaining sustained drug release. The tablets containing Duloxetine hydrochloride 150 mg were prepared by wet granulation technique using HPMC in the middle layer and barrier layers. Radar diagrams are provided to compare the performance of formulated tablets with the reference products, Effexor XR capsules. The granules ready for compression exhibited good flow and compressibility when aerosil was used in the intragranular and extragranular fractions. Monolayer tablets failed to give the release pattern similar to that of the reference product. The drug release was best explained by Weibull model. A unified Weibull equation was evolved to express drug release from the formulated tablets. Lactose facilitated drug release from barrier layers. Substantial water uptake and gelling of HPMC appears to be responsible for sustained drug release. The present study underlines the importance of formulation factors in achieving same drug release pattern from three strengths of Duloxetine hydrochloride tablets.

Key words: Duloxetine Hydrochloride Sugar Spheres#20, Hypromellose, Eudragit, Surelease, Ethyl cellulose, Poly Ethylene Gylcol-6000

Introduction

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that has been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage form. Nowadays most of the pharmaceutical scientists are involved in developing an ideal DDS. This ideal system should have advantage of single dose for whole duration of the treatment and it should deliver the drug directly at specific site. Scientists have succeeded to develop a system that can be as near to an ideal system and it encourages the scientists to develop controlled release system 1-4.



Plot between Drug Release Level & Time

The design of oral sustain drug delivery system should be primarily aimed to achieve the more predictability and reproducibility to control the drug release, drug concentration in the target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose 5-8.

Conventional drug therapy typically involves the periodic dosing of a therapeutic agent that has been formulated in a manner to ensure its stability, activity and bioavailability. For most of the drugs, conventional methods of formulation are quite effective. However some drugs are unstable and toxic and have a narrow therapeutic range, exhibit extreme solubility problems, require localization to a particular site in the body or require strict compliance or long-term use. In such cases a method of continuous administration of drug is desirable to maintain fixed plasma drug levels 9-10.

MATERIALS AND METHODS

Duloxetine Hydrochloride were obtained from Naprod Life Sciences, Mumbai Sugar Spheres#20, Hypromellose, Eudragit, Surelease, Ethyl cellulose, Poly Ethylene Gylcol-6000 were obtained from Sigma Aldrich, Bangalore.

FORMULATION OF DULOXETINEHCL SR COATED PELLETS:

Drug Loading

Pulverization:

Pulverize the Duloxetine HCL & sucrose through 0.5mm screen and collect the pulverized material into pre-labeled double lined poylthene bag HDPE container.

Sifting: Sift the sucrose, Aerosil, through #100 vibro sifter.

Blending: Transfer the pulverized and sifted material one by one in conta blender. Blend the material about 15 min at 12 RPM.

Binder solution: Take the purified water in container. And add Hypromellose, sucrose (syrup grade) in purified water under continuous stirring till the clear solution is obtained. Filter the clear solution through #200 nylon cloth into a cleaned container.

Drug Loading: Load the Sugar spheres (#22#24) into coating Load the Sugar spheres (#22#24) into coating pan and start the coating pan and allow thespheres to rotate. Adjust the spray gun atomization air pressure to 1.0-2.0 kg/sq cm. Start the peristaltic pump and adjust to 5-15 RPM. Start spraying the syrup solution by adjusting the gun distance (30-40cm). Continue spraying till the spheres become wet. Add drug blend in small quantities to the wet pellets in the coating pan until the spheres are free flowing. Adjust the peristaltic pump 15-40 RPM and continue the spraying of syrup solution and powder addition till the complete drug blend is exhausted. After completion of the process unload the wet drug pellets into trays in equal quantities and keep for drying.

Drying: Load the wet coated pellets into tray drier and load the trays into drier. Set the inlet temperature at 45±3ºC and maintain the bed temperature between 42º- 48ºc.

Sifting: Sift the dried pellets through #16 and collect 16# retained and passing separately into the poly bag. Sift #16 passing pellets through #20 and collect retains and passing separately into poly bag. The sifted pellets are collected into HDPE containers.

SR COATING FOR THE DRUG LOADED PELLETS:

PREPARATION OF COATING SOLUTION:

Pass the Isopropyl Alcohol through #200 Nylon cloths into the container. Dissolve, half quantity of the Ethyl cellulose in IPA with continuous stirring. Dissolve the PEG 6000 in purified water with continuous stirring in a separate container. Mix the above prepare Magnesium Stearate and PEG 6000 solution to Ethyl cellulose, continue this stirring for 15 min. After stirring, filter the solution through #200 nylon cloth into separate containers.

Formulation of Duloxetine Hydrochloride coated pellets:

Ingredients	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**
Duloxetine Hydrochloride	33	33	33	33	33	33	33	33
Sugar pellets	40	40	40	40	40	40	40	40
Aerosil	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60
Sucrose	12.0	11.52	15.02	16.86	12.52	14.66	12.66	9.80
HPMC	0.38	0.38	0.38	0.38	0.38	0.38	0.38	0.38
Water	QS	QS	QS	QS	QS	QS	QS	QS

***In-vitro* dissolution test**

For capsules place 1000ml of dissolution medium in each vessel and allow the medium to equilibrate to a temperature of 37±0.5ºC .place one capsules in each of the basket and operate the apparatus at 100 rpm for specific time. With draw10ml of the solution from each vessel and replace with equal volume of fresh dissolution medium at specific time intervals. Filter the solution through 0.45microns membrane filter and discard first few ml of the filtrate. Dissolution study was carried out in pH 6.8 buffer for 2nd, 6th, 12th, 18th and 20th hours and assay was done by HPLC method.

RESULTS AND DISCUSSION

In the present work Capsule dosage form containing Duloxetinehydrochloride ER coated pellets were prepared by using Drug layering solution method in pelletization technique and used for the treatment of Depression.

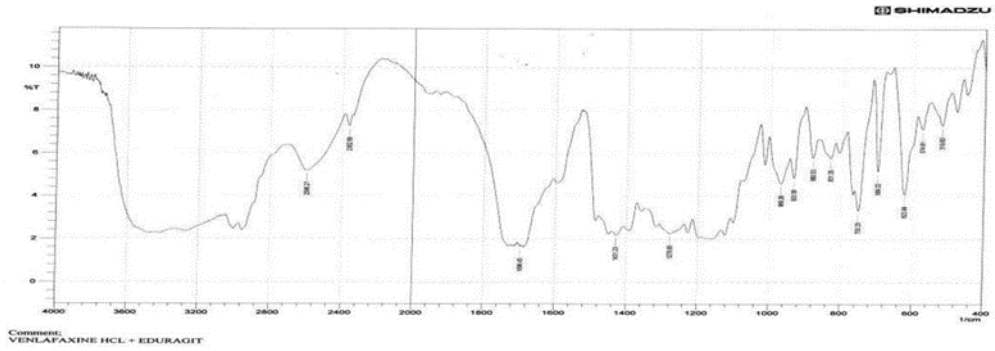
Preformulation

Preformulation data are vital for decision making on the choice of dosage form and excipients and essential for preceding it further for the development of dosage form.

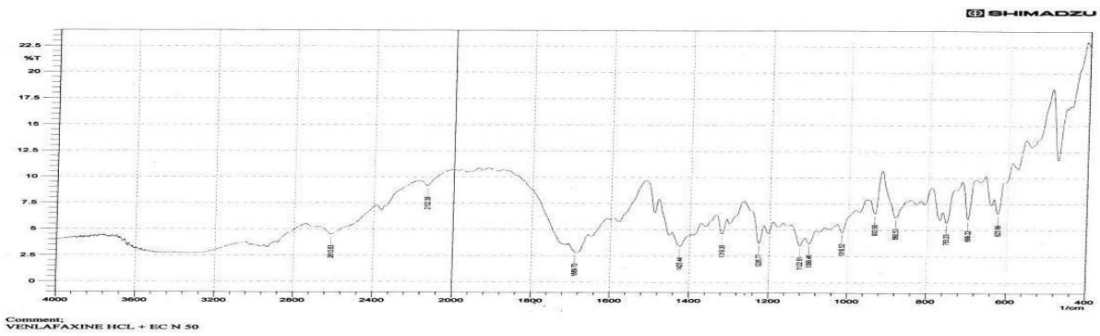
Characterization of active pharmaceutical ingredient and polymer

Drug (Duloxetinehydrochloride), polymers (Ethyl cellulose N50), (Eudragit and surelease) were characterized by using Fourier Transform Infra Red Spectroscopy.

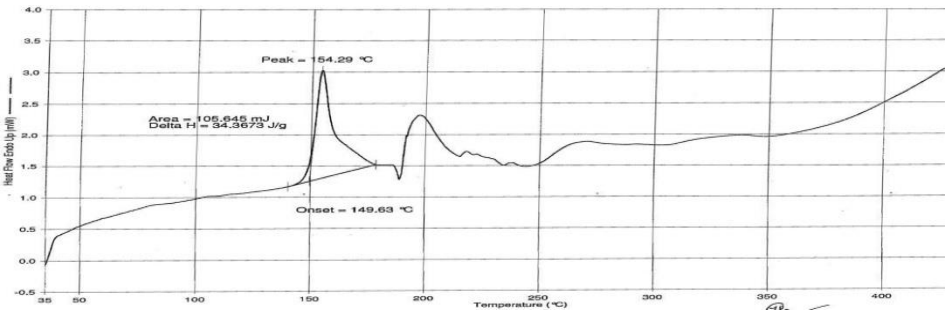
Duloxetinehydrochloride was analyzed under IR spectra and their results were produced in following figures. The mixture of API with Ethyl cellulose, API with Eudragit, API with Surelease, and their mixture were characterized through IR spectrum and their spectra were given in following figure. The resulted IR spectra were interpreted and presented. The results match the test sample when compared with reference standard.



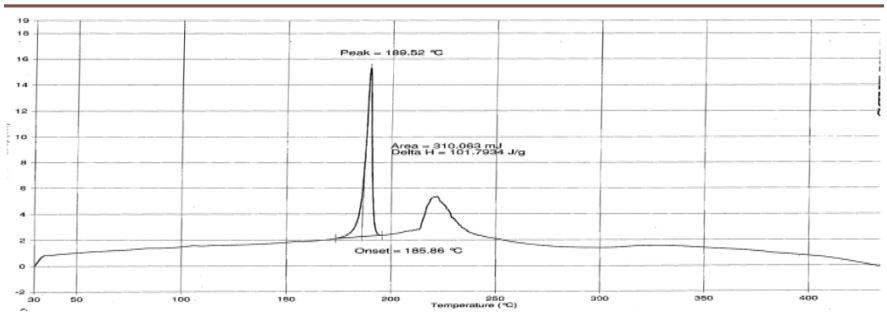
FTIR Spectrum of venlaflaxine Hydrochloride



FTIR Spectrum of optimized formulation



DSC SPECTRUM of pure drug and optimized formulation

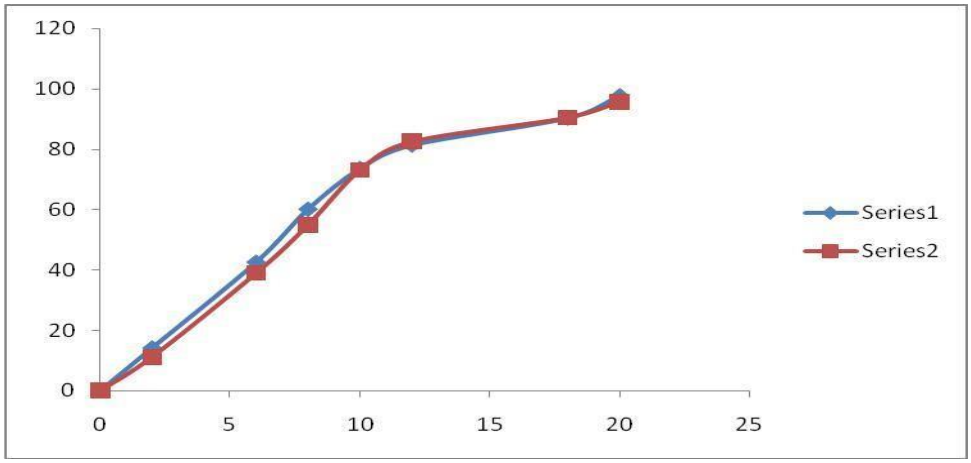


Evaluation of Sustained release Coated Pellets (F4- F11)

FORMULATION	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**
ANGLE OF REPOSE (degrees)	32.6	29.0	31.8	27.84	27.8	28.4	28.32	**29.87**
BULK DENSITY (gm/ml)	0.628	0.621	0.614	0.614	0.655	0.694	0.702	**0.66**
TAPPED DENSITY (gm/ml)	0.778	0.728	0.712	0.712	0.742	0.785	0.790	**0.703**
COMPRESSIBILITY INDEX (%)	19.2	14.6	13.7	13.06	11.7	11.5	11.1	**6.11**
HAUSNER'S RATIO	1.23	1.17	1.15	1.15	1.13	1.13	1.12	**1.06**
LOSS ON DRYING (%)	2.05	1.75	2.25	2.10	2.08	0.99	0.97	**0.85**
FRIABILITY (%)	0.214	0.175	0.326	0.563	0.459	0.523	0.143	**0.965**
DRUG	100.56	96.75	98.78	99.04	99.86	99.9	100.0	**100.02**

Evaluation of Duloxetine Hydrochloride SR Coated Capsules (F4-F11)

S. No	**Formulations**	**Weight variation in (mg) ± S.D**	**Drug content (%)**	**Cumulative % Drug content of 10 capsules**
1.	F4	227.8 ± 1.02	100.56	99.73
2.	F5	229.2 ± 0.07	96.75	98.00
3.	F6	226.9 ± 1.01	98.78	100.60
4.	F7	227.8 ±0.06	99.04	101.04
5.	F8	228.4 ± 1.0	99.86	99.97
6.	F9	225.9 ±1.02	99.9	99.21
7.	F10	227.0 ± 0.6	100.1	101.88
8.	**F11**	**227.0 ± 0.6**	**100.2**	**101.29**



In-Vitro Release Study of (F4) SR Coated Pellets with reference product

CONCLUSION

The active pharmaceutical ingredient DuloxetineHydrochloride was subjected to preformulation study, which encompasses the "Accelerated drug excipient compatibility study", and the results obtained with selected excipients showed good compatibility with DuloxetineHydrochloride drug.

Duloxetine Hydrochloride coated pellets were formulated by using commercially available sugar pellets and DuloxetineHydrochloride SR coated capsules were filled by automatic capsule filling machine with various excipients used during formulation . The optimization procedures aided in the stabilization of the formula and in the formulation of the DuloxetineHydrochloride modified release capsules.The stability of the capsules and pellet was determined by conducting "Accelerated stability testing" in 40°C ± 2°C / 75%

± 5%RH and 25ºC ± 2 ºC/ 60% RH ± 5% RH, 30ºC±2ºC/65±5%

RH conditions for 3 months as per ICH guidelines in HDPE containers. Finally after the duration, the product was analyzed for weight varation, content uniformity, assay and dissolution studies. By the stability studies, the formulated DuloxetineHydrochloride modified release capsules and pellets proved to be stable throughout the period of the storage. The DuloxetineHydrochloride Sustained release pellets were loaded in size 1 hard gelatin capsules. It showed good results in formulation of stable dosage. The dissolution profile of the prepared DuloxetineHydrochloride sustained release capsules were compared with that Duloxetine Hydrochloride modifiedrelease capsules (Effexor SR) of the product. The release was found similar to that of innovator. So the prepared product was said to be equivalent with innovator.When come to discussion of dosage form SR coated pellets in capsule showed better drug release. Sustained release pellets have minimum volume in size, greater surface area and more surface activity. The area of the drug loaded pellets release rate was also more. Because of Small size, pellets enter into the systemic circulation in very fast. Moreover there was no accumulation of drug in the body. Drug release rate was more.The release in the starting hours is controlled by increasing the concentration of Ethyl cellulose N-50 in the formulations in F10 formula and the plasticizer is also increased. It was observed that the release profile of the pellets were good by using ethyl cellulose polymer, when compared with the Eudragit's (independent), Eudragit's (dependent) L100 & Surelease. Finally I conclude that Sustained release pellets of formulation F11 has relevant drug release rate than Surelease, Polyacrylates and it has better stability, Bioavailability.

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