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ENTERIC RELEASE FORMULATION OF ACID-LIABLE DRUG DULOXETINE HYDROCHLORIDE

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ABSTRACT

The aim of the present study is to formulate and evaluate Duloxetine delayed release pellets. Duloxetine is a novel anti-depressant used widely for treatment of depression and generalised anxiety disorder, but it is having disadvantage of forming a toxic product of alpha-naphthol when comes in contact with 0.1N Hydrochloric acid. So in order to prevent toxic product formation and to promote the enteric release DR capsules has been formulated. The present research work was directed towards the development of a delayed release dosage form of Duloxetine in the form of capsules. In the present study polymers such as HPMC E5, HPMC Hp 55 was used as coating polymers which helps in providing delayed release. The dissolution studies of the dosage form was performed and analysed by HPLC. Different evaluation parameters such as drug-excipient compatibility by FT-IR, XRD, and DSC were done and *in-vitro* drug release was performed which showed dissolution profile as per specification. Different polymers are optimized on the basis of release pattern. The marketed formulation was evaluated for the *in-vitro* release studies and formulated product is compared with the marketed delayed release pellets.

KEY WORDS: Duloxetine hydrochloride, HPMC Hp55, multiple units' particulate system, delayed release

1. INTRODUCTION

An ideal drug delivery system provides treatment for acute diseases or chronic illness to the patients for many years. A number of oral dosage forms are available. Some are liquids (e.g., syrups, elixirs, tinctures, suspensions, and emulsions), whereas the most common ones are solids (e.g., tablets and capsules). Tablets and capsules are generally formulated to release the drug immediately after oral administration to hasten systemic absorption. These are called Immediate-release products. Other products like Modified-release dosage forms have been developed to release the drug at a controlled rate. The purpose is generally either to avoid contact with gastric fluids (acidic environment) or to prolong drug input in systemic circulation. Delayed release systems release a bolus of the drug after a predetermined time in a predetermined location, i.e. they do not release the drug immediately after ingestion, for example enteric-coated tablets, pulsatile-release capsules. 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 convenience means of drug administration. The release of drug from an oral dosage form may be intentionally delayed until it reaches the intestine. Enteric coatings are those which remain intact in the stomach, but will dissolve and release the contents once it reaches the small intestine. Their prime intension is to delay the release of drugs which are inactivated by the stomach contents or may cause nausea or bleeding by irritation of gastric mucosa.

2. MATERIALS AND METHODS

Duloxetine hydrochloride was obtained as a gift sample from Dr.Reddy's laboratories and all other excipients and chemicals used were of analytical grade. Drug loading has been performed on three formulations (F1, F2 and F3). Subcoating was done on the optimized batch F3 using different concentrations of HPMC E5. (F3.1, F3.2 and F3.3). The delayed release coating using HPMC HP55 was performed on optimized batch F3.3 (F3.3.1, F3.3.2, F3.3.3 and F3.3.4) (Table 1).

Method of preparation of enteric coated pellets:

Drug coated pellets: HPMC E5 was added to purified water under continuous stirring till clear solution was formed, to this solution, polyplasdone was added and homogenized until clear solution was formed. Talc and titanium dioxide was slowly added and dissolved in water separately with continuous stirring. Then both the solutions were mixed and duloxetine was slowly added and stirring was continued till uniform dispersion is formed. The drug containing solution was sprayed on to sugar spheres which were previously loaded into fluidized bed coater.

Barrier coated pellets: HPMC E5 was added to the purified water under continuous stirring for 45min to get a homogenous dispersion. Then the barrier coating solution was sprayed on to the drug coated pellets which were previously loaded in the fluidized bed coater.

Enteric coated pellets: Isopropyl alcohol and acetone were taken in the ratio of 1:1 in a stainless steel vessel. HPMC HP was added to this solvent and mixed for 10 minutes under continuous stirring. Cetyl alcohol and iron oxide red were added to the above solution under continuous stirring till homogeneous dispersion was formed. This suspension was sprayed on to the barrier coated pellets which were previously loaded in the fluidized bed coater.

Accelerated stability studies: Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutics and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and to establish a retest for the drug substance or a shelf life for the drug product and recommended storage conditions. As per ICH guidelines, the samples for stability analysis must be exposed to an environment of 40 ± 2˚C / 75 ± 5% RH for a period of 6 months. As per the standard protocol the samples must be analyzed at 0, 1, 2, 3 and 6 months time points. Accelerated stability studies were performed for the final optimized formulation. Samples are analyzed at 1, 2, 3,6 months time points.

3. RESULTS

Drug excipients compatibility study:

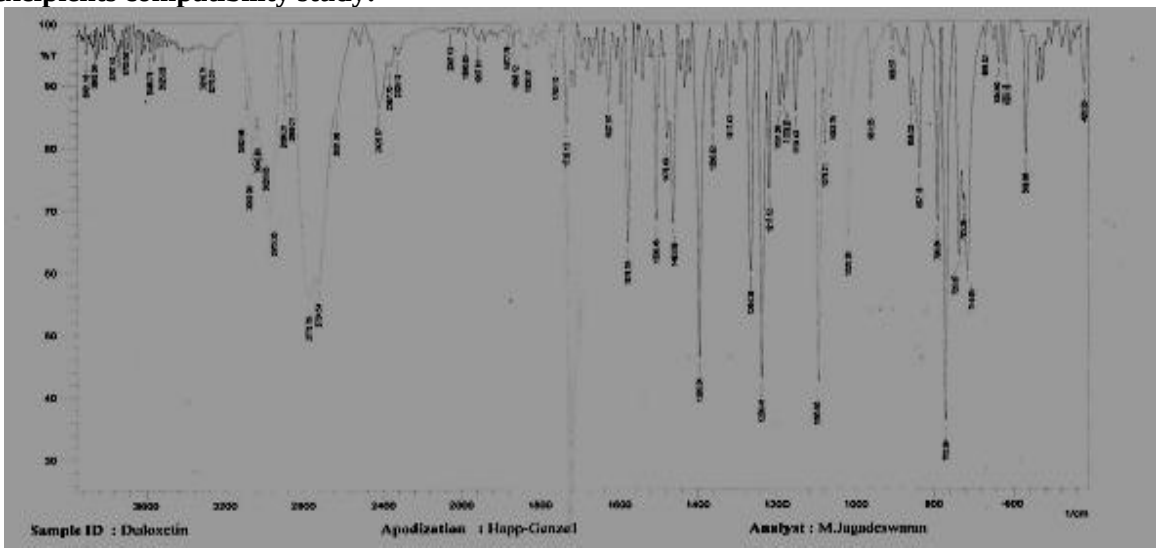

Figure.1.FT-IR spectrum of Duloxetine

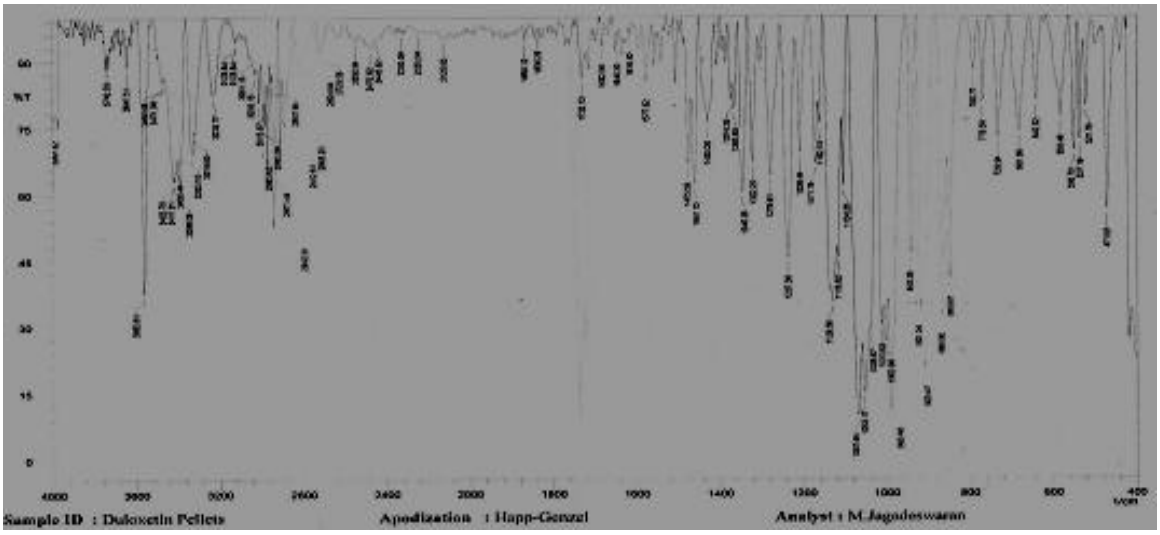

Figure.2.FT-IR spectrum of Duloxetine with excipients

Compatibility studies between Duloxetine and polymers were carried out by subjecting to I.R spectral studies using perkin fourier transform infrared spectrophotometer, Schimadzu.The samples were scanned under diffuse reflectance mold and plotted the graph by KBr pellet method and spectra were recorded in wave length region between 4000cm^{-1} to 400 cm^{-1}. In these spectra of Duloxetine, the physical mixtures of drug-polymer mixture, was shown in figure no1, 2. All identical principal peaks were observed in all cases, hence it was confirmed that an interaction do not exist in between the Duloxetine and polymers (HPMC).

Table.1.Formulation of Duloxetine hydrochloride pellets

Ingredients (mg)	F1	F2	F3	F3.1	F3.2	F3.3	F3.3.1	F3.3.2	F3.3.3	F3.3.4
Drug coating										
Duloxetine	43	43	43	-	-	-	-	-	-	-
Sugar spheres	122	122	122	-	-	-	-	-	-	-
INF-10	12	12	12	-	-	-	-	-	-	-
HPMC E5	10	--	8	-	-	-	-	-	-	--
HPMC 50	--	10	--	-	-	-	-	-	-	-
Talc	2.1	2.1	2.1	-	-	-	-	-	-	-
Titanium dioxide	2.3	2.3	2.3	-	-	-	-	-	-	-
Purified water	Q.s	Q.s	Q.s	-	-	-	-	-	-	-
Barrier coating										
HPMC E5	-	-	-	16	14	12	-	-	-	-
Purified water	-	-	-	Q.s	Q.s	Q.s	-	-	-	-
Enteric coating										
HPMC HP55	-	-	-	-	-	-	12	14	16	18
Acetone	-	-	-	-	-	-	Q.s	Q.s	Q.s	Q.s
IPA	-	-	-	-	-	-	Q.s	Q.s	Q.s	Q.s
Cetyl alcohol	-	-	-	-	-	-	1	1	1	1
Iron oxide red	-	-	-	-	-	-	0.6	0.6	0.6	0.6
Total weight	-	-	-	-	-	-	225	225	225	225

Evaluation of delayed release pellets:

Table.2. Optimization of drug coated pellets

Time (min)	Percentage drug release		
	F1	F2	F3
0	0	0	0
10	72	62	80
20	79	69	91
30	88	76	95
45	92	83	97
60	96	89	99

Table.3.Optimization of sub coated pellets

Time (min)	Percentage drug release		
	F3.1	F3.2	F3.3
0	0	0	0
10	64	68	76
20	72	75	81
30	81	79	86
45	87	82	88
60	90	86	93

Table.4.Comparative dissolution profiles for different formulations

Time (Min)	Percentage drug release in buffer stage			
	F3.3.1	F3.3.2	F3.3.3	F3.3.4
0	0	0	0	0
10	17.3	18.4	20.9	24.4
20	26.2	36.2	42.6	52.1
30	38.7	52.1	65.9	64.3
45	46.7	60.1	72.1	79.3
60	65.4	76.5	84.2	90.6

Table.5.Gastric resistance of different formulations

Formulations	Gastric resistance
F3.3.1	99.05
F3.3.2	98.03
F3.3.3	98.54
F3.3.4	99.31

Table.6. Different Parameters obtained for formulations

Formulations	Bulk density	Tapped Density	Moisture Content	Assay %w/w
F3.3.1	0.69	0.76	1.65	99.4%
F3.3.2	0.71	0.85	1.67	99.3%
F3.3.3	0.70	0.83	1.64	99.2%
F3.3.4	0.73	0.87	1.62	99.7%

Evaluation of innovator product

Assay: The assay of the Innovator was found to be 99.6±0.01%

Dissolution:

Table.7. Dissolution profile of Innovator Product

Time (min)	% drug release	Time (min)	% drug release
10	22.1	45	76.2
20	51.3	60	90.1
30	62.2	Gastric resistance	98.1

Table.8. Accelerated stability data of Optimized formulation

Tests	Specification	Duration of study		
		Initial	3m	6m
Description	Red color spherical pellets	Red color spherical pellets	Red color spherical pellets	Red color spherical pellets
Identification	The retention time of the principal peak obtained with the sample solution should correspond to that of working standard as obtained in the assay	Complies	Complies	Complies
M.C by K.F	Not more than 5.0%w/w	2.5%	2.56%	2.59%
Gastric resistance	Not less than 90% of labeled amount of duloxetine shall retain as residue after 2 hours in 0.1n hcl	99.5%	97.8%	97.1%
Dissolution in buffer	Not less than 70% of labeled amount of duloxetine shall dissolve in phosphate buffer of ph 6.8 in 45 minutes	79.5%	79.3%	78.5%
Assay	Not less than 16.5% & not more than 17.5%	17.3%	16.8%	16.3%

Discussion: sugar spheres are coated with the mixture of Duloxetine along with binder such as HPMC E5 and HPMC 50. The pellets were studied for drug release and the result indicate that formulation F1 containing 10 mg of HPMC E5 showed 72%, which is less than in house specification of 80% in 10 minutes. In F2 formulation the drug release was found to be 62% using HPMC 50. The F3 formulation containing HPMC E5 has 80% of drug release and was found to be above the limit. The optimized drug coated pellet F3 are coated with HPMC E 5 in three different ratios (F3.1, F3.2 and F3.3) where F3.1 showed 64% , F3.2 and F3.3 68% and 76% respectively. Hence F3.3 formulation was selected as optimized subcoating polymer. The subcoated pellets were coated with HPMC HP55 in four different ratios (F3.3.1, F3.3.2, F3.3.3 and F3.3.4). the result indicates the drug release was very poor and not within the limits when subcoated pellets were coated 12 and 14 mg(F3.3.1 and F3.3.2) and drug release was not delayed when pellets were coated with 16 mg (F3.3.3). Finally formulation containing HPMC HP 55 showed 90.6% of drug release (F3.3.4)which was compared to innovator.

CONCLUSION

From this it can be concluded that the duloxetine delayed release formulation containing 10% HPMC E5 (F3.3) & 15% HPMC HP 55 (F3.3.4)was found to be showing good release pattern and this can be used for future research in developing enteric release capsule formulation for acid liable drugs such as duloxetine

REFERENCES

AdhimoolamSenthil, ThakkarHardik Kumar Rajesh Bhai, Dave MehulkumarVinodBhai, Lad Tejas Bharat Bhai, Bhagya Lakshmi Battu, Formulation and evaluation of mucoadhesive microspheres, International journal of research journal of pharmacy, 2(4), 2011, 194-199,

Audrius Sveikata, Vita Danileviciute, Comtemporary approach to pharmacological and clinical aspects of novalantidepressatnts, Medicina, 38(12), 2002, 1147-1156.

Janicak PG, Davis JM, Preskorn SH, Principles and practice of psycho pharmacotherapy, 3rd Ed; Lippincot Williams and wilkins, 2001, 432 – 440.

Lopez C, Lykissa ED, Kammerer RC, Determination of Fluoxetine in dosage form, plasma and urine by gas chromatographic method using electron capture detector, Clin. Chem, 35(6), 1989, 1169 – 1172.

M.E.E shams, B.Arneth, C.Hiemke, A.Dragicevic, M.J.Muller, R.Kaiser, K.Lackner and S.Harrter, CYP2D6 polymorphism and clinical effect of the antidepressant Journal of Clinical pharmacy and Therapeutics, 31(5), 2006, 493–502.

Thomson, Physicians' desk reference, ThomsdonPdr, Montvale, NJ, 58th edition, 2004, 3413-3424.