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Formulation development and evaluation of duloxetine extended-release tablets

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Abstract

Duloxetine is an anti-depressant drug which is used in depression. The aim of present investigation was to prepare an ER tablet of duloxetine with similar dissolution profile matching to Effexor ER. An immediate release core tablet of 100mg was prepared and it was compression coated using HPMC matrix system. HPMC of three viscosity grades i.e., K4M, K15M, K100M and different concentrations of 15% polymer, 25% polymer, 35% polymer & 45% polymer were taken. With the above polymers by using wet granulation and direct compression process 11 formulations were prepared. The data obtained from in vitro drug release was used to determine the similarity factor between marketed and optimized product. Out of all F11 formulation (K15M 35% polymer) is optimized and is matching with the marketed product.

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Introduction

Duloxetine HCl is a structurally novel antidepressant drug, and is usually categorized as serotonin-norepinephrine reuptake inhibitor (SNRI), but it is referred as serotoninnorepinephrine-dopamine reuptake inhibitor (SNDRI) [1,2]. Its active metabolite, O-desmethylDuloxetine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Duloxetine and ODV have no significant affinity for muscarinic, histaminergic, or α-1 adrenergic receptors in vitro. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Duloxetine and ODV do not possess monoamine oxidase (MAO) inhibitory activity. Duloxetine is well absorbed and extensively metabolized in the liver. The halflife of Duloxetine was 5 to 7 hours so must be given two or three times to maintain adequate plasma concentration. The present work was carried out to develop extended release Duloxetine tablet to be given once daily. The main objective of the present work was to develop a swelling matrix type drug delivery platform system for Duloxetine HCl which will have dissolution profile similar to Effexor XR capsules. To develop a platform technology for Duloxetine sustained release tablets using compression coating as technique for controlling drug release. Drug loaded pellets of Duloxetine HCl were enrobed in a HPMC matrix by the compression coating technique. The cup: cap technology was used for the compression coating due to its novelty, easy of fabrication and excellent reproducibility [3-5].

Experimental work

Duloxetine IR Formulation [6-7]

The experimental work was performed in the following sequence: . Dissolution profile of the innovator product (Effexor XR) was performed to determine the target. 2. Drug loading of Duloxetine HCl on to sugar pellets as per standardized method. Preparation of coating material formulations using different viscosity grade polymers each at 15%, 25%, 35% and 45% concentration for compression coating by the wet granulation method. Characterization of the granules. Compression coating of drug loaded pellets with coating formulations. Preparation of coating material formulations using different viscosity grade polymers each at 15%, 25%, 35% and 45% concentration for compression coating by the direct compression method. 6. Compression coating of drug loaded pellets with coating formulations [7]. Dissolution profiles for compression coated tablets and in 0.1N HCl as per the USP method.

Analytical results

Standard curve for Duloxetine

Standard curve for Duloxetine were done by ultraviolet spectroscopy within the range of 200 – 400nm.

Preparation of Hydrochloric acid

8.5 ml of concentrated hydrochloric acid was diluted with distilled water and the volume was made upto 1000ml with

distilled water. PH (1.2) was adjusted with dilute hydrochloric acid.

Preparation of Duloxetine Hcl Standard Stock Solution in buffer solution,

PH 6.8

A Standard Solution of Duloxetine HCL was prepared by dissolving accurately weighed 100 mg of Duloxetine HCL with little quantity of phosphate buffer solution, pH 6.8 in a 100 ml volumetric flask. The volume was made up to 100 ml with phosphate buffer solution, pH 6.8 to obtain a stock solution of 1000µg/ml. Accurately weighed quantity of Duloxetine (100 mg) was dissolved in little quantity of phosphate buffer solution, pH 6.8, and volume was made up to 100ml. From this, 1ml of solution was pippeted out into a volumetric flask and volume was made upto 100ml. Appropriate aliquots were taken into different volumetric flask and volume was made up to 10ml with phosphate buffer solution, pH 6.8,so as to get drug concentration of 4 to 24µg/ml. The absorbances of these drug solutions were estimated at λ_{max} 226 nm

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany (Alpha T). The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm^{-1} to 550 cm^{-1}.

Pre formulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose.

Table 01: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

Measures of powder compressibility

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Table 02: Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Composition of the formulation [8-9]

Table 03: Formulation of Duloxetine Core Pellets

S.No	Ingredients	F1	F2	F3	F4
1	Duloxetine	33	33	33	33
2	Sugar Pellets (#20#24)	35	35	45	40
3	Aerosil	1	1	0.8	0.60
4	Sucrose	8.02	13.58	7.35	12.02
	Binder solution				
5	Sucrose	4	10.5	4.45	3.00
6	Hypromellose (HPMC 606)	0.38	0.4	0.4	0.38
7	Purified water	QS	QS	QS	QS

From formulation (F1) to formulation (F4), excepients were altered at different concentration to obtain desired pellets, while the active pharmaceutical ingredient was kept constant in all the formulations.

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	Binder solution				
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6	Hypromellose (HPMC 606)	0.38	0.4	0.4	0.38
7	Purified water	QS	QS	QS	QS

From formulation (F1) to formulation (F4), excepients were altered at different concentration to obtain desired pellets, while the active pharmaceutical ingredient was kept constant in all the formulations.

Table 04: Formulation of Duloxetine HCL coated pellets [10-12]

S.No	Ingredients	F4	F5	F6	F7	F8	F9	F10	F11
1	Duloxetine	33	33	33	33	33	33	33	33
2	Sugar Pellets (#20#24)	40	40	40	40	40	40	40	40
3	Aerosil	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60
4	Sucrose	12.02	11.52	15.02	16.86	12.52	14.66	12.66	9.80
	Binder solution								
5	Sucrose	3.00	3.00	3.00	3.00	3.00	3.00	3.20	3.20
6	Hypromellose (HPME 606)	0.38	0.38	0.38	0.38	0.38	0.38	0.38	0.38
7	Purified water	QS	QS	QS	QS	QS	QS	QS	QS
	SR COATING								
8	Eudragit INDEPENDENT	5	10	—	—	—	—	—	—
9	Eudrragit l 100(dependent)	—	—	6	—	—	—	—	—
10	SURELEASE INDEPENDENT	—	—	—	3.13	9	---	---	---

11	Ethyl cellulose N-50	___	___	____	___	___	8.02	7.13	10.0
12	P.E.G-6000	1.0	0.5	1	0.34	0.5	0.34	0.34	0.34
13	Magnesium stearate	4	1	1	2.69	1	1.64	2.69	2.68
14	I.P.A	QS	___	___	___	___	___	QS	QS
15	Purified Water	QS	QS	QS	QS	QS	QS	QS	QS
		99.9	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Results

Table 05: 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 CONTENT (%)	100.56	96.75	98.78	99.04	99.86	99.9	100.01	**100.02**

Table 06: Sieve Analysis for Sustained release Coated Pellets

S.NO	SIEVE NO	PERCENTAGE OF SAMPLE RETAINED IN EACH SIEVE (%)							
		F4	F5	F6	F7	F8	F9	F10	F11
1.	16	9.1	10.9	11.2	12.4	13.4	11.8	12.4	**12.6**
2.	20	20.9	29.1	29.0	30.4	42.8	46.3	52.2	**52.2**
3.	24	70.0	60.0	60.8	57.2	43.8	41.9	35.4	**35.2**
4.	Pan	-	-	-	-	-	-	-	**-**

Table 07: Evaluation of Duloxetine HCL 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**

Table 08: Dissolution profile of SR Coated Pellets with Reference product Formulations (F4-F11)

S.No	Time in hrs	Percentage drug release								
		Effexor 75mg	F4	F5	F6	F7	F8	F9	F10	F11
1	0	0	0	0	0	0	0	0	0	**0**
2	2	14.2	13.6	33.6	11.2	10.2	22.3	19.5	12.6	**10.2**
3	6	42.6	22.7	55.3	39	21.2	42	35	23.6	**24.9**
4	8	60.2	46.9	75.6	55	32.1	56.9	52.35	47.8	**33.5**
5	10	73.7	67.6	86.4	73.2	60.3	72.6	70.45	68.3	**62.9**
6	12	81.4	76.1	98.9	82.6	69.6	79.7	78.9	78.1	**79.8**
7	18	90.4	81.3	ND	90.6	76	87.4	85.3	83.2	**85.5**
8	20	97.8	91.1	ND	95.8	83.1	96.6	95.3	94	**96.2**

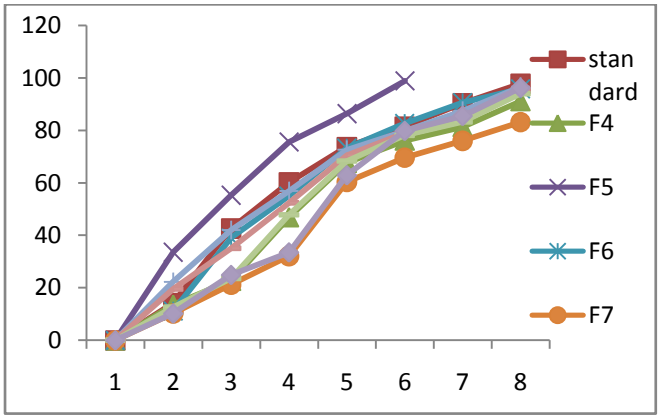

Fig 01: Dissolution profile of SR Coated Pellets with Reference product Formulations (F4-F11)

Discussion [13-14]

Formulation F4 SR coated pellets with 5% w/v of Eudragit (independent) produced 91.1% of release in buffer medium and also it is in continued with indiscriminate medium. So, the formulation F5 was coated with 10% Eudragit and this coating results in fast drug releasing within 10 hours in buffer medium. By observing the previous trails, than decided to take pH dependent polymer like Eudragit L100 as it is soluble in pH 6-7, as we have our official medium is also with in this range. In the formulation F6, 95.8% of drug released, the result was improved when compared with F4 & F5. But in this trail the polymer has changed because as our reference product shows pH independent release profile so that, we decided to the use of pH independent polymer. Hence formulation F7 was tried with 3.13% of surelease as SR coating polymer and the acquired result was 83.1% of Duloxetine HCL release. As above results were not satisfactory, surelease retarding the release of Duloxetine HCL in Buffer medium when compared with the other formulation. So, the alternate SR coating polymer Ethylcelluolse was decided to apply in the further formulation.

Formulation F8 was coated with 9.0% of surelease to the core pellets and the result was obtained as 96.6%. To retard the drug release more than the formulation F7 the concentration of surelease has been increased. To retard the drug release with ethylcelluolse the concentration was decided to take equal to (or) less than the concentration of surelease. Hence, formulation F9 & F10 was tried with 5.13% & 7.13% and Duloxetine HCL was released and observed desired range in phosphate buffer & the optimized batch was taken with ethycelluolse.

From the above observation, formulation F4 to F7 does not complies with desired drug retard in the phosphate dissolution medium and the continuous buffer stage dissolution was performed but not satisfactory. Formulation F8 and F9 had a better drug retarding property so the process was carried to next continuous pH 6.8 phosphate buffer stage for 20 hours. F9 & F10 showed the good sustained characters when compared with the F4 to F7. But the formulation F11 showed good release data. When compared to F10, formulation F 11 has shown good release tendency like the reference product. Finally by observing the release profile of both F10 & F11 both these trails were taken for the indiscriminate medium analysis.Formulation F4- F11 was designed by SR coating the core pellets of optimized formulation different SR coating polymers such as Surelease, Ethylcelluolse and Eudragits. The micromeritic properties such as bulk density, tapped density, angle of repose, hausner's ratio, and Compressibility index were studied. The angle of repose for the formulations F4-F11 ranges from 32.6o – 29.87o which depicts excellent flow character. Bulk density ranges from 0.628 gm/ml-0.66gm/ml. Tapped density for the enteric coated formulations F4-F11 lies between 0.778gm/ml-0.703 gm/ml. Hausner's ratio for enteric coated pellet formulations (F4-F11) ranges from 1.23gm/ml-1.06 m/ml .The values shows the property of excellent flow character. Percentage of Compressibility index for the formulations F4-F11was found to be 19.2, 14.6, 13.7, 13.06, 11.7, 11.5, 11.1 and 6.11 respectively. These values demonstrates the excellent flow character of formulations F4-F11Sieve analysis was performed in a sieve shaker with a set of sieves (16, 20, and 24) to determine the particle size and its

frequency of distribution. Percentage of sample retained in each sieve was calculated. As the pellets are SR coated the size of the pellets is slightly greater than the core pellets. the percentage of sample retained in each sieve (16, 20, and 24) are greater than core pellets. The pellets are smooth and uniform. Maximum percentage of sample retained in sieve no: 20. From the results the size of the pellets lies between 1.40-1.00 mm.

The friability for coated pellets were checked and it ranges from 0.214-0.965% w/w and the values depicts friability is within IP limit which is not more than 1% w/w, indicating the sufficient mechanical integrity and strength of prepared pellets.Loss on drying for the formulations F4-F11 ranges from 2.05-1.97 % .The values were within 1% and complies within IP limit.Drug content of formulations F4-F11 was found to lie between 100.56% to 100.02% .The results shows all formulation containing drugs were within the limit (95-105%) as per IP.The Sustained release coated pellets were filled in "1" size capsules and checked for weight variation .The coating was done up to 15% of weight gain of total weight of core pellets. The average weight of each capsule ranges from227.8±1.02 to 227.0±0.6. The formulations F4-F11 was observed to be within I.P limit ± 5%.

Assay was performed for randomly selected 10 capsules from each trial. The values range from 100.56- 100.2%. The results shows all the capsules of each trials containing drug were within the limit (95 - 105%) as per I.P.

To ensure the consistency of dosage units, each unit should have drug content within a narrow range around the label claim. Therefore test for content uniformity is performed. .Ten capsules randomly selected from each trial (F4-F11), Contents were removed and drug content present in each capsule is calculated. The average of ten capsules is calculated . the results show all the capsules were within the limit (95-105%) as per I.P.The dissolution studies for the formulations F4-F11 was performed in capsules filled with enteric coated pellets.

Conclusion

Based on the results concluding that the Sustained release pellets of formulation F11 has relevant drug release rate than Surelease, Polyacrylates and it has better stability, Bioavailability.

References

1. Lachman L, Liberman HA. The Theory and Practice of Industrial Pharmacy. 3rd ed., Varghese Publishing House, Bombay: 293-330.
2. Remington. The Science and Practice of Pharmacy. 21st ed, Vol. 1; 2005: 889-905.
3. Ansel H, Nicholas G. Ansels Pharmaceutical dosage forms and drug delivery system.9th edn. Lippincott Williams and Wilkins: 225-256.
4. Gartlehner G, Gaynes BN, Hansen RA et al. Comparative benefits and harms of second-generation antidepressants: background paper for the American College of Physicians. Ann Int. Med Nov 18, 2008; 149(10): 734-50.
5. Hamilton M. A rating scale for depression, Journal Neural Neurosurgery Psychiatry. 1960; 23: 56 63.
6. American Psychiatric Association. Arlington (VA): Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Part B: Background Information and Review of Available Evidence: c2010.
7. Keith S (2006). Advances in psychotropic formulations. Prog Neuro psychopharmacol Biol Psych; 30:996-1008.
8. Ric AM, Moyer A, Haskins JT, Andree TH, Husbands GE (1991). Biochemical, Neurophysiological and behavioral Effects of Wy- 45,233 and other identified Metabolites of the Antidepressant Duloxetine . Drug Dev Res; 23: 191-199.
9. Simona JS, Aguair Lm (2004). Extended Release Duloxetine in relapse prevention for patients with major Depressive disorders, J Psychiatr Res; 38: 249-257
10. Troy S.M, Parker VD, Fruncillo RJ, Chiang ST (1995). The Pharmacokinetics of Duloxetine when given in a twice –daily regimen, J Clin Pharmacol; 35:404-409.
11. Shinde Anilkumar. J (2008). Gastro retentive drug delivery system-An overview, Pharmainfo.net; 6(1).
12. R. Colombo, P.S. Bettini, N.A. Peppas, Swellable matrixes for Controlled drug delivery; gel-layer behavior, mechanism and optical performance Pharm. Sci. Technol. Today.3(2000) 198-204
13. Marabathuni VJ, Dinesh P, Ravikumar R, Yamini P, Kiran PS, Hussain SP, Rao CM. Chitosan based sustained release mucoadhesive buccal patches containing amlodipine besylate (AMB). Asian J Res Pharm Sci. 2017 Jun 28;7:97-104.
14. Marabathuni VJ, Bhavani M, Lavanya M, Padmaja K, Madhavi N, Babu P, Rao CM. Formulation and evaluation of mouth dissolving Tablets of carbamazepine. Asian Journal of Pharmacy and Technology. 2017;7(3):137-43.