Research Article

Formulation Development and Evaluation of Dapoxetine Hydrochloride Tablets Approved for the Treatment of Premature Ejaculation

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ABSTRACT

Dapoxetine Hydrochloride a selective serotonin reuptake inhibitor is a new chemical entity for the treatment of premature ejaculation. Since no systematic studies on design and development of Dapoxetine hydrochloride tablets are available in literature, we propose to develop a suitable formulation to characterize in vitro release profile of Dapoxetine hydrochloride. The aim of the present study was to formulate various formulations of immediate release tablets of Dapoxetine Hydrochloride using different excipients by direct compression and wet granulation method. The granules and tablets of Dapoxetine HCl were evaluated for various pre and post compression parameters like Angle of repose, Compressibility index, Hausner's ratio, Tablet hardness, Thickness, Friability, and chemical parameters. Punches of different size were used to obtain the desired shape, ease of swallowing of tablets, to improve aesthetic value in terms of appearance and shape of tablets. To match dissolution profile of test formulation with innovator, drug particle size is reduced from D_{90}-158 µ to D_{90}-45 µ, which resulted in an increased surface area exposed to the dissolution medium. Final formulation was evaluated for multimedia dissolution in three different media and dissolution data was found satisfactory. Accelerated stability studies conducted for 2 Months at 40°C and 75% RH and were found within specification.

Keywords: Dapoxetine HCl, Dissolution, Immediate Release Tablets, Micronized API, Particle Size, Premature Ejaculation.

INTRODUCTION

The oral route of drug administration is the most popular and successfully used for conventional delivery of drugs. It offers the advantages of convenience, ease of administration, greater flexibility in dosage form design, ease of production, and low cost.[1] Immediate release drug delivery system are based on single or multiple-unit reservoir or matrix system, which are designed to provide immediate drug levels in short period of time. Immediate release drug delivery is desirable for drugs having long biological half life, high bioavailability and lower clearance.[2] The current investigation is concerned with formulation and optimization of oral immediate release tablets of Dapoxetine HCl. Premature ejaculation is the most common male sexual complaint. Off-label oral selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed for the treatment of premature ejaculation. Dapoxetine is a short-acting SSRI specifically designed for on-demand use.

Dapoxetine hydrochloride a selective serotonin (5-HT) reuptake inhibitor is a novel drug approved by CDSCO on 13th November, 2010 for the treatment of premature ejaculation in men of 18 to 64 years of age. Premature ejaculation is one of the commonly encountered male sexual disorders in clinical practice as it is estimated to occur in 4-39% of men.[3] Dapoxetine shares a similar mode of action with other SSRIs. Dapoxetine inhibits the serotonin reuptake transporter, with minimal inhibitory effects at the nor epinephrine and dopamine reuptake transporters. The chemical name is (+)-(S)-(N), *N*-dimethyl-(a)-[2-(1-napthalenyloxy)ethyl]-benzene methanamine hydrochloride. Its structure is similar to fluoxetine. The molecular weight of Dapoxetine is 341.88 and is a water-soluble compound. The pKa is 8.6 and it is charged at a physiological pH of 5.87. After administration, Dapoxetine is rapidly absorbed. Rate of absorption of Dapoxetine is slightly decreased by food and Elimination of Dapoxetine is biphasic. The initial half-life for 30 and 60 mg doses of Dapoxetine is approximately 1.31 and 1.42 hours respectively and 18.7 and 21.9 hours for the terminal half-life, respectively. Longer-acting SSRIs such as fluoxetine and paroxetine are absorbed much slower than dapoxetine.[4] In the present study there are different formulations of immediate release tablets of Dapoxetine hydrochloride, which is an effective alternative for the treatment of premature ejaculation due to its rapid action and short half life. The objective of the development programme was to develop a generic tablet which is robust, stable, and an acceptable formulation when compared to reference original product thereby fulfilling the requirement of essential similarity to the marketed product.

MATERIALS AND METHODS

Dapoxetine hydrochloride was procured from Emcure Pharmaceuticals Ltd. Maharashtra, Lactose Monohydrate was received from DFE Pharma, Microcrystalline cellulose (Avicel 101), Microcrystalline cellulose (Avicel 102), Croscarmellose Sodium (Ac-di-sol), were procured from FMC Biopolymers, and Aerosil was obtained from EVONIK Pharma, and Opadry Grey from Colorcon.

Preformulation studies

Drug excipients compatibility study

Preformulation can be defined as the investigation of physical and chemical properties of drug substance alone and when combined with excipients.

Table 1: Drug excipients compatibility study

Condition/Time period		Related substance	
55°C	15 days	✓	
Sample		% Impurity	
		% Highest Unknown	% Total Impurities
Dapoxetine HCl		BDL	BDL
Dapoxetine HCl + Microcrystalline Cellulose 101		BDL	BDL
Dapoxetine HCl + Lactose monohydrate		BDL	BDL
Dapoxetine HCl + Croscarmellose Sodium		BDL	BDL
Dapoxetine HCl + Colloidal Silicon dioxide		BDL	BDL
Dapoxetine HCl + Magnesium Stearate		0.03	0.03
Dapoxetine HCL + Hydroxy propyl cellulose		BDL	BDL
Dapoxetine HCl + Titanium Dioxide		BDL	BDL
Dapoxetine HCl + Black oxide of Iron		0.04	0.04
Dapoxetine HCl + Yellow oxide of Iron		0.03	0.03
Dapoxetine HCl + Opadry Grey		0.04	0.04

*BDL – Below detection Limit

Analysis for related substances performed after 15 days on the plain API and API-Excipient Mixture. This study was performed to establish the compatibility of Dapoxetine hydrochloride in its solid formulations with various excipients. The various factors affecting Dapoxetine hydrochloride stability were studied using high performance liquid chromatography (HPLC). It was found that binary 1:1 mixtures of Dapoxetine hydrochloride and excipients are stable at 55°C. The study reveals that mixtures with Opadry Grey, Magnesium Stearate and Black oxide of iron show slight increase in impurity with API but no significant change observed.

Preparation of immediate release tablets of Dapoxetine hydrochloride

Immediate release tablets of Dapoxetine hydrochloride were prepared by wet granulation method. Dapoxetine hydrochloride and lactose monohydrate co-sifted through 30# sieve, microcrystalline cellulose (Avicel 101) and Croscarmellose sodium was co-sifted through 40# sieve. All the above sifted materials transferred to Rapid Mixer Granulator and mixed for 10 minutes. Granulation was done in Rapid Mixer Granulator by adding Purified water slowly to get dough mass, mixing continued to get desired end point of granulation. Wet granules were dried in FBD at inlet air temperature of 50°C till LOD of dried granules obtained not more than 2.00 % w /w. Sizing of dried granules was done through 20# sieve. Croscarmellose sodium, Avicel PH 102, and Colloidal silicon dioxide were sifted through 40# sieve. Pre-lubrication was done by mixing sifted granules with sized granules in blender for 10 minutes. Magnesium stearate was sifted through 60# sieve and lubrication was done by mixing above pre-lubricated granules with magnesium in blender for 5minutes.The lubricated granules were compressed into tablets on a 16 station rotary compression machine to get a tablet of 103 mg and 206 mg weight for 30 mg and 60 mg strength respectively.

Preparation of coating solution

In Purified water Opadry Grey was dispersed under continuous stirring. Stirring continued for 45 minutes. This dispersion was filtered through nylon cloth.

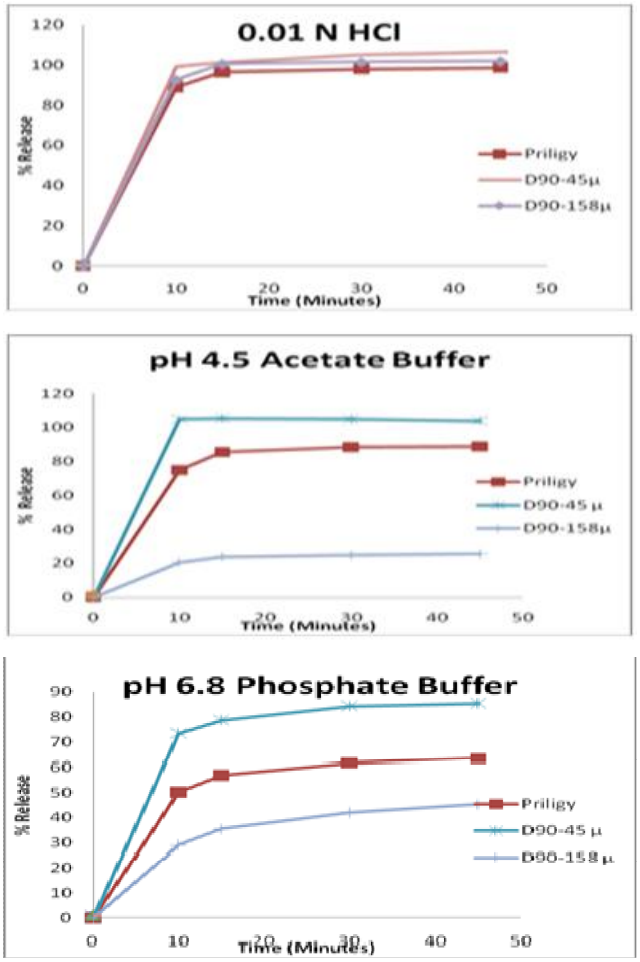

Figure 1: Graphs showing multimedia dissolution results Dapoxetine HCl Tablets 60 mg

Accelerated Stability Study

The tablets of final formulation (F7) were subjected for stability at accelerated conditions (40°C/75% RH).

Tablets were packed in aluminium blister pack and charged for Stability study at accelerated condition

(40°C/75% RH) for 2 months in a humidity chamber. Samples withdrawn after 2 month showed no significant change in appearance, assay, related substances and % drug release. The results of accelerated stability studies are shown in Table 7. Result of accelerated stability studies indicates that the formulation is stable.

Table 2: Formulations of Dapoxetine hydrochloride Tablets

Ingredients	Formulations						
	F1	F2	F3	F4	F5	F6	F7
	30 mg strength				60 mg strength		
Method →	DC	WG	WG	WG	WG	WG	WG
Dry Mix	(mg/tab)						
Dapoxetine HCl	33.581	33.581	33.581	33.581	67.163	67.163	67.163
Lactose monohydrate (Super Tab 30GR)	25.850	25.850	25.850	25.850	51.70	51.70	51.70
Microcrystalline cellulose (Avicel 101)	-	29.569	29.569	29.569	59.137	59.137	59.137
Croscarmellose Sodium (Ac-di-sol)	-	2.00	2.00	2.00	4.00	4.00	4.00
Binder							
Purified Water	-	Q. S.	Q. S.	Q.S.	Q.S.	Q.S.	Q.S.
Pre-lubrication							
Croscarmellose Sodium (Ac-di-sol)	2.00	2.00	2.00	2.00	4.00	4.00	4.00
Microcrystalline cellulose (Avicel 102)	39.069	7.50	7.50	7.50	15.00	15.00	15.00
Colloidal Silicon Dioxide (Aerosil)	1.5	1.5	1.5	1.5	3.00	3.00	3.00
Lubrication							
Magnesium Stearate	1.00	1.00	1.00	1.00	2.00	2.00	2.00
Coating							
HPMC 6 CPS	2.462	2.462	2.462	-	4.924	4.924	4.924
PEG 6000	0.3	0.3	0.3	-	0.6	0.6	0.6
Titanium dioxide	0.3	0.3	0.3	-	0.6	0.6	0.6
Iron oxide black	0.025	0.025	0.025	-	0.003	0.003	0.003
Iron oxide yellow	0.003	0.003	0.003	-	0.049	0.049	0.049
Opadry Grey	-	-	-	3.090	-	-	-
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Q.S. – Quantity sufficient

Table 3: Evaluation of Dapoxetine HCl Powder blend

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index	Hausner's ratio	Angle of Repose
F1	0.37	0.49	24.4	1.32	35
F2	0.44	0.59	25.4	1.34	29
F3	0.45	0.63	28.5	1.4	28
F4	0.49	0.67	26.8	1.36	30
F5	0.42	0.55	24	1.316	32
F6	0.48	0.60	25.0	1.25	33
F7	0.48	0.60	25.0	1.25	33

Table 4: Evaluation of immediate release film coated tablet of Dapoxetine HCl

Formulation code	Weight (mg)	Thickness (mm)	Hardness (Kp)	Disintegration Time
F1	106±3	3.60±0.1	8.5±2	8 Min
F2	106±2	3.60±0.1	7.5±2	8 Min 22 sec
F3	106±2	3.10±0.1	7.5±2	1 Min 50 Sec
F4	106±2	3.10±0.1	6.5±2	1 Min 40 Sec
F5	212±3	4.06±0.1	10.0±2	2 Min 30 Sec
F6	211±3	4.07±0.1	9.6±2	3 Min
F7	212±3	4.07±0.1	9.5±2	3 Min

Table 5: Multimedia dissolution results of Dapoxetine HCl 60mg with respect to particle size

Dapoxetine HCl Tablets 60 mg - Dissolution Data									
Media	**0.1 N HCL**			**4.5 Acetate buffer**			**6.8 Phosphate buffer**		
Strengths	60	60	60	60	60	60	60	60	60
	Priligy	F5	F6	Priligy	F5	F6	Priligy	F5	F6
Particle size	NA	D_{90}-158µ	D_{90}-45µ	NA	D_{90}-158µ	D_{90}-45 µ	NA	D_{90}-158µ	D_{90}-45 µ
Time (min)	**% Cumulative release**								
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
10	89.0	92.7	99.2	74.9	20.6	104.7	50.2	29.2	73.4
15	96.6	100.6	101.3	85.4	23.9	105.3	56.8	35.5	78.7
30	98.0	101.5	104.9	88.4	24.9	104.8	61.6	42.1	84.3
45	98.8	101.9	106.3	88.8	25.6	103.9	63.4	45.3	85.4

Table 6: Multimedia dissolution profiling of Dapoxetine HCl Tablets 30 mg

Time in minutes	0.1 N HCL		pH 4.5 Acetate Buffer		pH 6.8 Phosphate Buffer	
	% Cumulative Release					
	Priligy	Test	Priligy	Test	Priligy	Test
0	0	0	0	0	0	0
10	89.0	97.9	74.9	94.4	50.20	68.8
15	96.6	98.3	85.4	100.2	56.88	75.2
30	98.0	99.0	88.4	101.8	61.69	80.7
45	98.8	101.6	88.8	102.3	63.42	82.6

Table 7: Results of accelerated stability study

Test name		Testing period (months)		
		Initial	1	2
Formulation		F7		
Description		A grey colored, film-coated tablets	A grey colored, film-coated tablets	A grey colored, film-coated tablets
% Assay		100.11	100.33	99.91
Dissolution (% Drug release)	Mean	104.9	98.2	99.4
	Min	102.7	95.8	97.7
	Max	106.6	100.4	100.6
Related Substance				
Any unspecified impurity (%)		0.050	0.042	0.06
Total impurities (%)		0.108	0.134	0.15

RESULTS AND DISCUSSION

Dapoxetine HCl immediate release tablets were formulated by wet granulation method and two strength of Dapoxetine 30 mg and 60 mg were developed as compliance with innovator. Trials were taken on two different sizes of punches i.e. 6 mm and 6.5 mm. Coating of tablets was done initially with in- house coating system and then to reduce the process time and improve the coating quality, Opadry Grey was used to coat the tablets. During formulation development first trial F5 was taken with API of particle size D_{90}-158. Dissolution results of both F5 and innovator was evaluated in 0.01 N HCl and observed no significant difference as Dapoxetine HCl is soluble in 0.01 N HCl (71 mg/ml 7.1%) but in case of 4.5 acetate buffer and 6.8 phosphate buffer dissolution was slow as compared to innovator. Dissolution rate of a compound is directly related to its exposed surface area. Therefore micronized Dapoxetine hydrochloride was used for formulation, which resulted in an increased surface area to the dissolution medium and ultimately increases the dissolution rate. Formulations with micronized Dapoxetine hydrochloride exhibit markedly increased rate of dissolution as compared to non-micronized formulations. Dapoxetine hydrochloride particle size was reduced from D_{90} -158 µ to D_{90} - 45 µ. Multimedia dissolution study was performed for formulation F6 and it was observed that no significant difference was seen in 0.01 N HCl as earlier stated but in case of pH 4.5 acetate buffer and pH 6.8 phosphate buffer, noticeable increase in dissolution result was observed as particle size of Dapoxetine Hydrochloride was reduced. Result of final formulation containing particle size of Dapoxetine hydrochloride D_{90}-45 µ was compared with innovator and results were found satisfactory. Formulation F7 is a reproducible trial of optimised formulation. Multimedia dissolution study was performed for lower strength also.

CONCLUSION

On the basis of above observation it can be concluded that by reducing the particle size of Dapoxetine HCl we can improve its dissolution. By reduction in particle size there is an increase in surface area which results in increase of dissolution rate. Thus optimization of particle size for Dapoxetine hydrochloride was done and formulation was developed. Dissolution test results were compared with innovator and it was observed that final formulation shows satisfactory results.

REFERENCES

1. Gupta MM, Mahida Mayur, Formulation Development and Evaluation of Immediate Release Tablets of Antihypertensive Drug Olmesartan Medoxomil, The Pharma Innovation 2(3), 2013, 68-79.
2. Natarajan R, Vaishnani Rohit, Rajendran NN, Formulation and Evaluation of Immediate Release Tablets of Paroxetine HCl Using Different Superdisintegrants, International Journal of Research in Pharmaceutical and Biomedical Sciences, 2(3), 2011, 1095-1099.
3. Sangkum Premsant, Badr Rhamee, Serefoglu Can Ege, Hellstrom jG, Wayne, Dapoxetine and the treatment of premature ejaculation" Translational Andrology and Urology, 2(4), 2013.
4. Kanani VV, Gohil VP, Muralikrishna KS, Deshmukh A**,** Design and Validation of Dissolution Profile of Dapoxetine HCL by Using Spectrophotometric Method in Dosage Form, Inventi Rapid: Pharm Ana and Qual Assur, 1, 2012.
5. Modi B Nishit, Dresser J Mark, Simon Mary, Lin Denise, Desai Dhaval, Gupta Suneel, Single- and multiple-dose pharmacokinetics of Dapoxetine hydrochloride, a novel agent for the treatment of premature ejaculation, The Journal of Clinical Pharmacology , 46(3), 04/2006, 301-309.
6. Buvat Jacques, Tesfaye Fisseha, Rothman Margaret, Rivas A David, Giuliano François, Dapoxetine for the treatment of premature ejaculation: results from a randomized, double-blind, placebo-controlled phase 3 trial in 22 countries, European urology, 55(4), 01/2009, 957-967.
7. The Merck Index An encyclopaedia of chemicals drugs and biological, fifteenth edition, published by The Royal Society of Chemistry, 2013, 2821.
8. Sweetman SC, Ed., Martindale: The Complete Drug Reference, 34th edition, Pharmaceutical Press, London, UK, 2011, 2386.
9. Anderson KE, Pharmacokinetic and Pharmacodynamic features of Dapoxetine, a Novel Drug for On Demand, Treatment of Premature Ejaculation, BIU, 97, 2006, 311-315.
10. Sathe M. Pradeep, Raw S. Andre, Ouderkirk A. Larry, Yu X. Lawrence, Hussain S. Ajaz, Drug Product Performance, In Vitro Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Rockville, Maryland, U.S.A., 187-209.
11. Film Coating Process Considerations for the Application of High Productivity, High Solids Concentration Film Coating Formulations, Opadry II Colorcon.

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