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Formulation and evaluation of lamotrigine extended release tablets

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ABSTRACT

The present study was to develop once-daily extended release tablet of Lamotrigine, an Anticonvulsant. It is a phenyl triazines derivative showing effective anti-convulsant properties mainly used in effective in preventing seizure spread in the maximum electroshock (MES). The tablets were prepared by the wet granulation method.. The aim of the current study was to develop and optimize a simple matrix system of the model drug (BCS Class-II) using minimum possible excipients, to release the drug in a controlled fashion.Core tablets of model drug (F1 – F12) were successfully prepared by direct compression method, Mannitol SD200 & different grades of HPMC, Xanthan gum, Surelease and Magnesium stearate as excipients by direct compression method. The F11 formulation is the best formulation out of 12 formulations, the F11 contains HPMC k4m and metalose polymers, they maximum drug release and it follows Higuchi model

Introduction

Formulation and evaluation of Lamotrigine extended release tablets. The aim of the current study was to develop and optimize a simple matrix system of the model drug (BCS Class-II) using minimum possible excipients, to release the drug in a controlled fashion.In recent years, significant efforts have been devoted to develop oral extended release formulations based on matrix drug delivery.The objectives of the present study are to carry out preformulation studies to define the nature of the drug substance and develop frame work for drug combination with pharmaceutical excipients in the dosage form.To design a suitable matrix system for the model drug using different polymers and excipients.To optimize the formulations in order to achieve the desired release profiles. Evaluation of drug loaded matrix tablets for physical integrity.In-vitro evaluation of optimized formulation for the release characteristics.

Materials And Methods

Lamotrigine procured by Micro Advance Research centre,Bangalore,Lactose,HPMC K4M,HPMCE5,HPMC K100 LV, Xanthangum gifted from Zydus Cadila,Ahmedabad

Formulation Of Lamotrigine Er Tablets

Following ingredients were selected for formulation development of matrix tablets based on literature search and pre-formulation studies.

Formulation process:

General method for preparation of extended release lamotrigine tablets:

Matrix tablets of lamotrigine were prepared by wet granulation process. Different grades of three different classes of rate retarding polymers-HPMC, Xanthan gum and Surelease and metalose were chosen. Starch and lactose was used as diluent. Magnesium stearate was used as lubricant. The method was chosen as direct compression.

Evaluation of Compressed Tablets

Determination of Thickness and diameter:

The shape and dimensions of compressed tablets were determined by the type of tooling used during the compression.

Method:

Twenty tablets were randomly selected from formulations and thickness was measured using Vernier caliper. It was expressed in millimeter and average was calculated. The tablet thickness should be within the limits of ± 5%.

Determination of Weight variation:

Uniformity of weight was determined by USP method.

Method:

Twenty tablets were selected randomly and weighed. Average weight of the tablets was determined. These tablets were weighed individually and the weight variation was determined. The percent deviation was calculated using the following formula. The limits are mentioned in the below table as per USP.

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Determination of Mechanical strength of tablets Hardness:

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. It indicates the ability of a tablet to withstand mechanical shocks while handling and transportation.

Method:

Ten tablets were randomly selected from each formulation and hardness of the same was determined in terms of KP.

Friability:

Friability is the loss of weight of tablet in the container/package, due to removal of fineparticles from the surface. This In-process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation and shipment.

Method:

About 6.5 g tablets (W initial) were transferred into Roche friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were dedusted and weighed again (W final). The percentage friability was calculated by

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The percent friability was determined using the following formula:

% Friability = 100 (1-$W_{initial}$/ W_{final})

$W_{initial}$= Initial weight of tablets

W_{final} = Final weight of tablets after 100 revolutions

% Friability of tablets less than 1 % are considered acceptable.

Procedure to Estimate drug content:

Four tablets were powdered. The powdered sample equivalent to 10mg of drug was transferred to a 100ml volumetric flask. Required amount of pH 7.0 Phosphate buffer was added to dissolve drug and remaining volume was made up to 100ml with pH 7.0 Phosphate buffer, sonicate for 60 minutes and filter the solution. From the filtrate, 1ml was transferred to 10ml volumetric flask and the volume was made up to 10ml pH 7.0 Phosphate buffer. The sample was analyzed against blank by UV spectrophotometer at 249 nm.

$$\text{Assay} = \frac{\text{Drug content (practically)}}{\text{Drug content (Theoretically)}} \times 100$$

Drug excipients Compatibility:

Thermal properties of drug & polymer (EUDRAGIT, HPMC, PEO grades) were investigated using a METTLER differential scanning calorimeter thermal analysis controller with an intracooler-2 cooling. About 3 to 5 mg of product was placed in perforated aluminum sealed 50-µl pans, and the heat runs for each sample was set from 20°C to 300°C at 20°C/min, under an inert environment using nitrogen. The apparatus was calibrated using pure metals like indium with known melting points and heat of fusion (ΔH fusion).

In vitro drug release studies:

Dissolution tests were performed in a USP Dissolution Tester Apparatus I, II and III at 37 ± 0.5°C. For the developed formulations of the drug (n=3), dissolution tests were carried out in two media - 0.1 N HCl, and pH 7.0 phosphate buffer with under the following conditions given in table 16.

Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to zero order, first order, Higuchi square root and korsmeyerpeppas model. The criteria for selecting the most appropriate model were chosen on the basis of goodness of fit test.

The samples withdrawn were filtered through Millipore PVDF filters 0.45µM and drug content in each sample was analyzed after suitable dilution (if required) using a validated UV spectroscopic method at 249 nm.

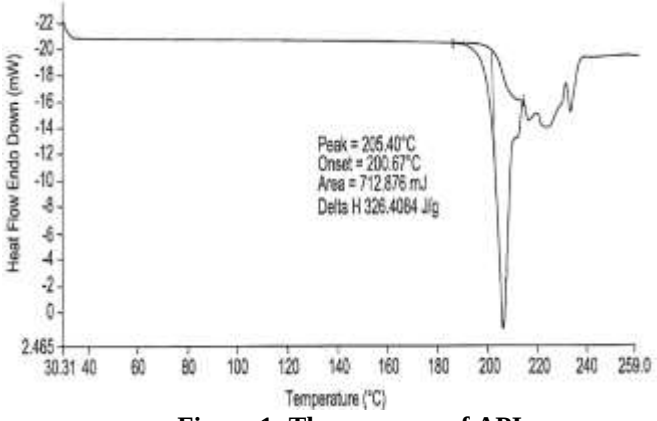

Figure 1: Thermogram of API

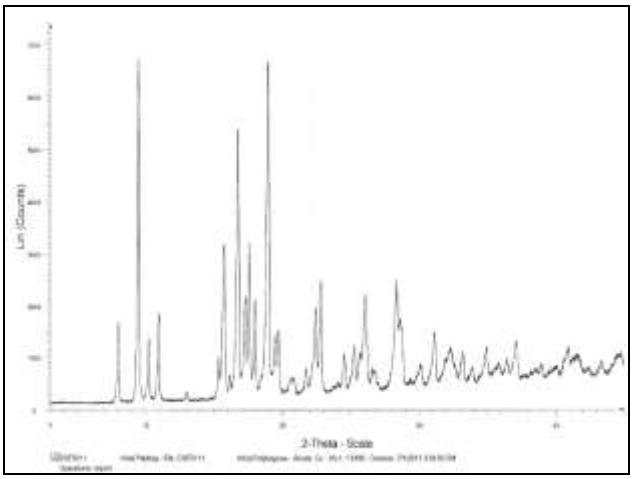

Figure 2: XRD pattern of lamotrigine

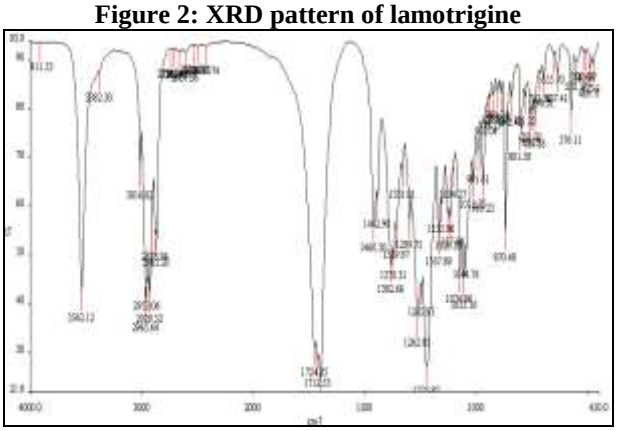

Figure 3: FTIR Spectrum of Pure Drug-Lamotrigine

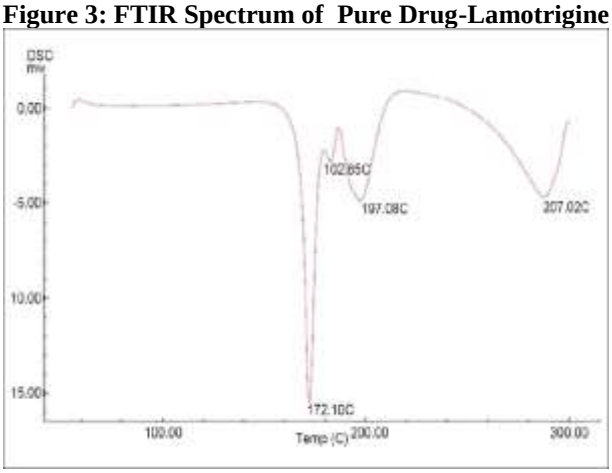

Figure 4: DSC thermogram of Drug

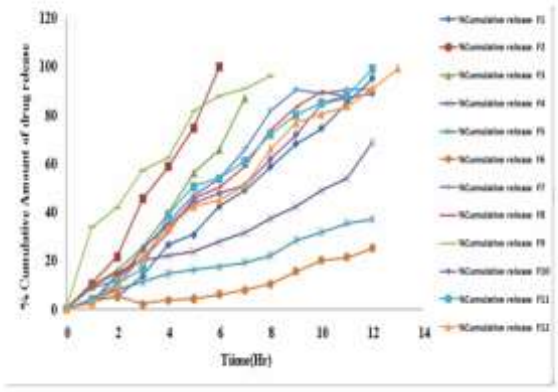

Figure 5: Dissolution Profile

Table 1: Composition of extended release lamotrigine tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Lamotrigine	100	100	100	100	100	100	100	100	100	100	100	100
Lactose	45	45	45	15	15	15	15	35	35	35	35	35
Starch	40	40	40	40	40	40	40	40	40	40	40	40
HPMC k4m	50	-	-	30	30	30	30	30	30	30	30	30
HPMC E5	-	50	-	-	-	-	-	30	-	-	-	-
HPMC K100 LV	-	-	50	-	-	-	-	-	30	-	-	-
Xanthangum	-	-	-	50	-	-	-	-	-	-	-	30
Chitosan	-	-	-	-	50	-	-	-	-	-	-	-
Surrelease	-	-	-	-	-	50	-	-	-	30	-	-
Metalose	-	-	-	-	-	-	50	-	-	-	30	-
Magnesium stearate	10	10	10	10	10	10	10	10	10	10	10	10
Aerosil	5	5	5	5	5	5	5	5	5	5	5	5
Total tablet weight	250	250	250	250	250	250	250	250	250	250	250	250

Table 2 USP specification for tablet weight variation

Average weight of tablet	Percentage weight variation
130 mg or less	10 %
More than 130 mg and less than 324 mg	7.5 %
324 mg or more	5 %

Table 3. Dissolution parameters

S.No	Parameters	Acidic medium	Alkaline medium
1	Dissolution apparatus	USP XXIV apparatus no. I (Basket type)	USP XXIV apparatus no. I (Basket type)
2	Temperature	$37^0C \pm 0.5^0C$	$37^0C \pm 0.5^0C$
3	Paddle speed	100 rpm	100 rpm
4	Dissolution medium	0.1 N HCl	pH 7.0 phosphate buffer
5	Volume of dissolution medium	900ml	900ml
6	Volume of sample removed	8 ml	8 ml
7	Volume of dissolution medium replaced (Sink)	8 ml	8 ml
8	Sampling interval	1 and 2 hr	3^{rd}hr to 12^{th}hr

Table 4: Particle size determination of lamotrigine

Sieve Mesh Number	Sieve Size Opening(µm)	Mass of Sample Retained on Each Sieve(g)	Percentage of Sample Retained on Each Sieve (%)	Cumulative Percentage of Sample Retained on Each Sieve (%)
20	841	0.64	12.8	12.8
40	420	0.87	17.4	30.2
60	250	2.03	40.6	70.8
80	177	0.77	15.4	86.2
100	149	0.29	5.8	92.0
120	125	0.25	5.0	97.0
Pan	-	0.10	2.0	99.0

Table 5 : Solubility data of pure drug

Ph	Solubility (mg/mL)
Distilled water	1000mg
Acid buffer (pH 1.2)	786mg
Phosphate buffer (pH 7.0)	841mg

Table 6: Flow and powder properties of Lamotrigine

Parameters	Value obtained
Bulk density (gm/cm3)	2.05
Tapped density (gm/cm3)	2.37
Compressibility Index (CI) %	13.5
Hausner's ratio (HR)	1.15
Angle of repose (θ)	22.7

Table 5: FTIR peaks and their functional groups of lamotrigine

Functional Group	IR range (cm-1)	Peak observed (cm-1)
Usually sharp O-H	3200-3550	3542.12
		3382.30
= C-H & = CH2	3020-3100	3026.02
CH3, CH2 & CH	2850-3000	2953.06
		2929.52
		2865.20
C-H	2690-2840	2736.39
C=O (saturated aldehyde)	1720-1740	1724.35
C=O (saturated ketone)	1710-1720	1712.53
		1710.58
CH2 & CH3	1350-1470	1460.30
		1442.98
OH bending	1330-1430	1382.66
		1370.31
		1359.87
		1331.01
C=O	1210-1320	1299.75
		1262.05
O-H bonded	970-1250	1245.93
		1223.87
C-N	1000-1250	1167.89
O-H bonded	970-1250	1155.96
		1126.53
		1117.16
		1104.27
		1074.96
		1055.16
		1044.76
		1013.75
=C-H & = CH2	880-995	991.61
		969.25
		952.04
= CH2	780-850	842.41
		801.58

Table 7 : Characterization of the blend

Formulation number	Bulk Density	Tapped Density	Carr's Index	Hausner ratio	Angle of repose
F2	0.55±0.25	0.64±0.16	26.21±0.34	1.16±0.22	35.5±0.36
F3	0.49±0.16	0.57±0.23	14.04±0.33	1.163±0.42	33.2±0.12
F4	0.48±0.11	0.55±0.42	12.72±0.13	1.14±0.35	32.4±0.44
F5	0.5±0.22	0.58±0.26	13.79±0.16	1.16±0.36	33±0.36
F6	0.53±0.35	0.61±0.42	13.11±0.42	1.15±0.42	32.1±0.13
F7	0.49±0.15	0.55±.36	10.9±0.41	1.12±0.35	33.5±0.36
F8	0.53±0.36	0.61±0.42	13.11±0.23	1.15±0.5	32.1±0.25
F9	0.53±0.14	0.66±0.46	19.69±0.11	1.24±0.42	31.8±0.36
F10	0.51±0.42	0.65±0.11	21.53±0.32	1.27±0.36	35.4±0.23
F11	0.54±0.45	0.61±0.5	11.47±0.42	1.12±0.13	32.5±0.42
F12	0.52±0.12	0.65±0.13	20±0.35	1.25±0.11	33.1±0.45

Table 8: Characterization of tablets

Formulation code	Weight variation	Hardness	Friability	Thickness	Content uniformity
F1	251±0.23	6.4±0.26	0.72±0.12	2.6±0.21	99.28±0.25
F2	249±0.5	6.3±0.15	0.68±0.2	2.6±0.5	97.16±0.36
F3	247±0.21	6.7±0.26	0.69±0.01	2.4±0.32	101.1±0.15
F4	252±0.32	6.6±0.5	0.66±0.13	2.45±0.25	97.68±0.24
F5	246±0.24	6.7±0.29	0.68±0.34	2.4±0.42	99.41±0.42
F6	248±0.26	6.9±0.42	0.65±0.32	2.38±0.24	98.19±0.36
F7	251±0.42	6.8±0.22	0.67±0.11	2.36±0.36	102.6±0.48
F8	250±0.15	7.1±0.33	0.65±0.29	2.36±0.48	99.5±0.28
F9	250±0.35	6.8±0.22	0.7±0.22	2.59±0.22	99.6±0.5
F10	249±0.26	6.7±0.12	0.68±0.11	2.6±0.36	98.4±0.24
F11	248±0.23	6.5±0.23	0.59±0.09	2.62±0.12	97.68±0.12
F12	247±0.39	6.7±0.20	0.52±0.13	2.58±0.32	97.06±0.36

Table 9: Comparison of prepared tablet with marketed product

Time (hrs)	Optimized (F11)	Marketed (LAMICTAL XR)
0	0	0
1	4.3	6.2
2	10.2	12.6
3	16.8	20.56
4	38.8	35.7
5	50.7	44.1
6	54	49.34
7	61	58.16
8	72	67.91
9	80	74.1
10	84.8	83.15
11	88	86.47
12	99	91.4

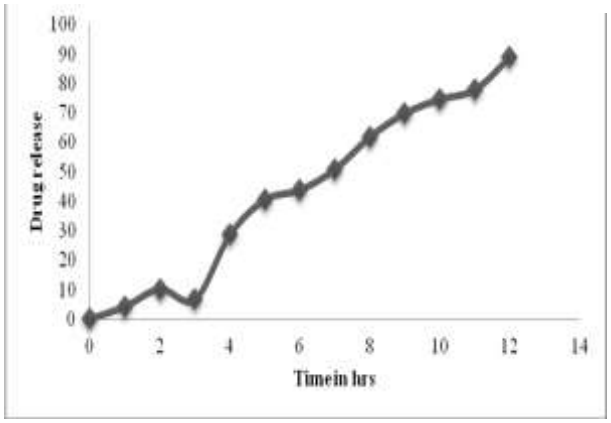

Figure 6: Dissolution profile of F11

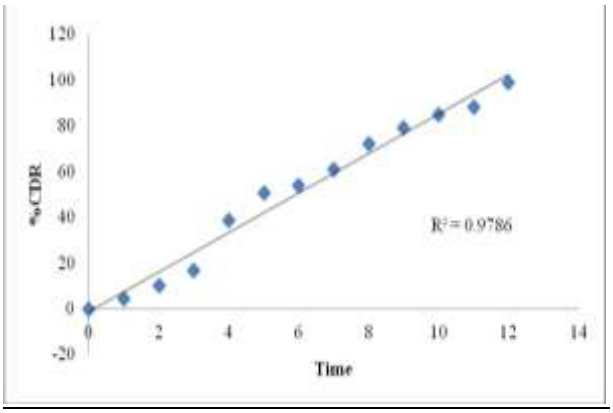

Figure 7: Zero order plot for F11

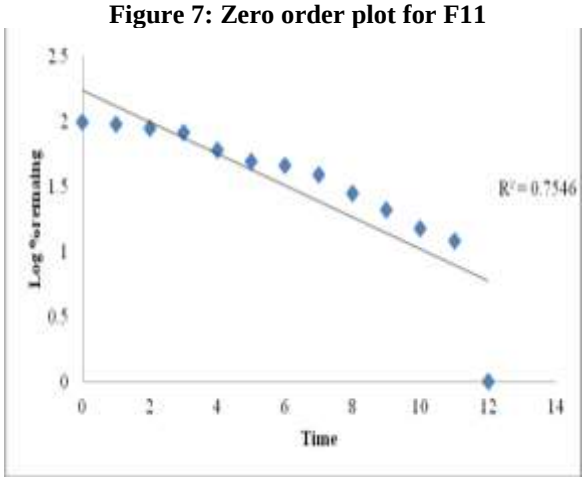

Figure 8: First order plot for F11

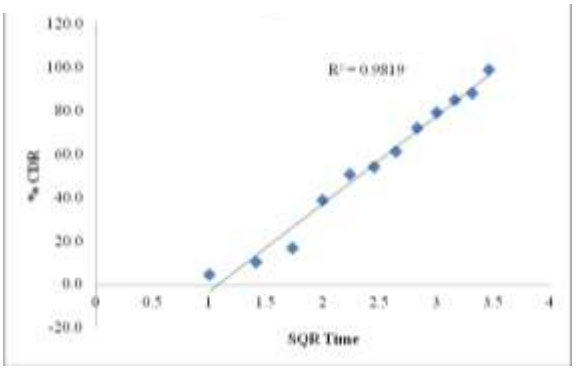

Figure 9: Higuchi plot for F11

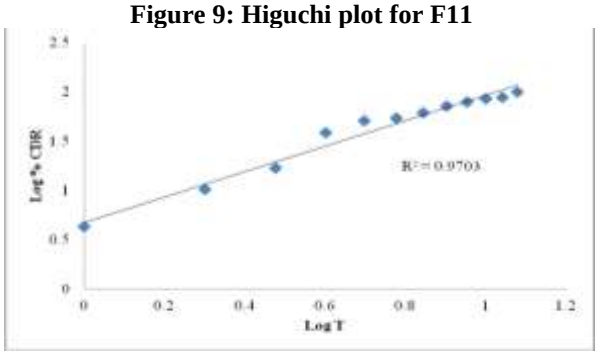

Figure 10: Korsemeyer Peppas plot for F11

Comparision of prepared lamotrigine ER tablets with Marketed product

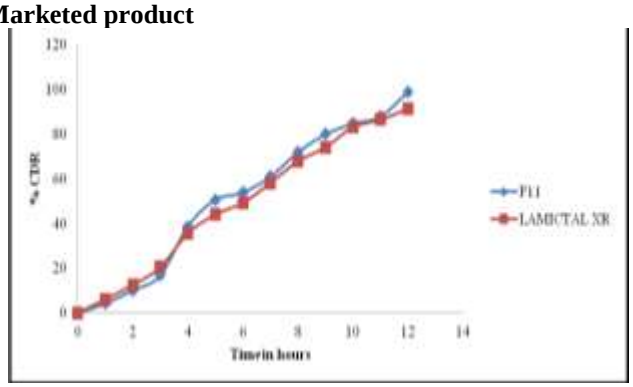

Figure 11: Comparision with marketed product

Conclusion

Optimized formulations for lamotrigine were developed and evaluated for pharmacopoeial and non-pharmacopoeial tests. The test results were within the limits. Drug release from the optimized formulation (F11) was found to be independent of pH of the medium and agitational intensity. Effects of polymers were also checked on the drug release. Drug release from the developed formulation (F11) follows Higuchi model

and kors meyer peppas model with a diffusion coefficient (n value) of 1.287 indicating the drug release mechanism to be Super Case II transport.

References

1. Mamidala RK, Ramana V, Lingam M, Gannu R, Yamsani MR. Factors influencing the Design and Performance of Oral Sustained/Controlled Release Dosage Forms. Int J Pharm Sci and Nanotechnology. 2009; 2: 583-593.
2. Jantzen GM, Robinson JR. Sustained and controlled drug delivery systems. In: Modern Pharmaceutics, 3rd edn. New York: Marcell Dekker, Inc; 1995. p.575-609.
3. Chib R, Sonker M, Hooda A. Design, Formulation and Evaluation of Sustain Release Dosage Form. Drug Invention Today. 2010; 2: 397-399.
4. U.S.Pharmacopoeia 29, National Formulary 24. U S Pharmacopoeial Convention. Washington DC: Board of Trustees Publication. 2008; Vol 1.
5. Lachman L, Liberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy, 3rd edn. Bombay: Varghese Publishing House; 2005. P. 171-195.
6. Brahmankar DM, Jaiswal SB. Controlled drug delivery. In: Biopharmaceutics and Pharmcokinetics – A treatise, 6th edn. New Delhi: VallabhPrakashan; 2006. P. 347-353.
7. Srivastav M, Prabhakar B, Omray A. Extended Release Tablet Technologies- Matrix, Melt Granulation and Multiparticulates: An Overview. International Journal of Universal Pharmacy and Life Sciences. 2011; 1: 331-354.
8. Sampath KP, Bhownik D, Chandira M, Tripathi KK. Innovations in Sustained Release Drug Delivery System and its Market Opporutinities. J Chem. Pharm Res. 2010; 2: 349-360.
9. Kamboj S, Gupta GD. Matrix Tablets: An Important Tool for Oral Controlled Release Dosage forms. 2009; 7, www.pharmainfo.net/review.
10. Jain NK. Controlled Drug Delivery System Progress. In: Controlled and Novel Drug Delivery System. Delhi: CBS Publishers, VallabhPrakashan; 2002: 54-58.
11. Tajane SR, Kholwal BB, Suryawanshi SS, Tarkase KN. Current Trends in Pulsatile Drug Delivery Systems. Int J Pharm Sci. Res. 2012; 3(2): 358-366.
12. Remington, Extended Release and Targeted Drug Delivery System. In: The Science and Practice of pharmacy, 21st edn. USA: Lippincott Williams and Wilkins; 2006. P. 903-913.
13. Aulton ME. Modified Release per oral Dosage form. In: Pharmaceutics: The Science of Dosage form Design, 2nd edn. USA: Churchill Livingstone; 2005. P.291-295.
14. Siahi MR. Design and evaluation of 1 and 3 layer matrices of Verapamil for sustained release. AAPS Pharm Sci Tech 2005; 6.
15. Modi SA, Gaikwad PD, Bankar VH, Pawar SP. Sustained release drug delivery system: A review. Int J Pharma Res. Dev. 2011 Feb; 2(12):147-160.
16. Banker GS, Rhodes CT, Sustained and controlled drug delivery systems. In: Modern Pharmaceutics, 4th edn. New York: Marcel Decker Inc; 2002. P. 501-513.
17. Kumar V, Damien B, Potdar AR, "Designing of stability programme", The Eastern Pharmacist, 1992; 29-23.
18. drugs.com/kapvay.html [cited Mar 22]
19. netdoctor.co.uk/smoking-cessation/medicines/zyban.html [cited Mar 22]
20. rxlist.com/toprol-xl-drug.htm [cited Mar 22]
21. virtualmedicalcentre.com/drugs.asp?drugid=2418&title=Kapanol [cited Mar 22]
22. Sajeev C, Punnarao R, Ranendra SN. Development and Evaluation of Oral Controlled Release Formulations of Celecoxib using Optimization Techniques. The Pharmaceutical Societyof Japan. 2006; 126: 505-514.
23. Abdelkar H, Abdalla OY, Salem H. Formulation of Controlled-Release Baclofen Matrix Tablets: Influence of some Hydrophilic Polymers on the Release Rate and in-vitro evaluation. AAPS PharmSciTech. 2007; 8: E1-E11.
24. Barakat NS, Elbagory IM, Almurshedi AS. Controlled-Release Carbamazepine Granules and Tablets Comprising Lipophilic and Hydrophilic Matrix Components. AAPS PharmSciTech. 2008; 9: 1054-1062.