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Der Pharmacia Sinica, 2011, 2 (4): 78-86

Der Pharmacia Sinica
ISSN: 0976-8688
CODEN (USA): PSHIBD

Formulation and evaluation of Deflazacort controlled release tablets

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ABSTRACT

The objective of the study was to develop matrix tablets for oral controlled release of Deflazacort. In present study controlled release tablets of deflazocart were successfully developed using wet granulation method. To achieve better patient compliance and for prolonged release of drug from the dosage form. Formulation development of diffusion based controlled release matrix tablets of Deflazacort using polymers such as HPMC K100M, Ethylcellulose 50CPS and HPC and their combinations and selection of the best formulation among them. Flow properties – Angle of repose, loose bulk density, tapped density and also % Carr's compressibility was determined for all the formulations which showed good flow property. The thickness found uniform, hardness and friability values of all the formulation tablets prepared by wet granulation method were within the limits and found to be mechanically stable. In vitro dissolution results showed that % of drug release was prolonged in formulation F12 that is up to 12 hours when compared to other formulations. This indicates that the drug released from the formulation F12 was effective up to 12 hours.

Key words: Deflazacort, hydroxypropyl methylcellulose (HPMC), HPC, Ethyl cellulose.

INTRODUCTION [1-5]

Controlled release (CR) technology has rapidly emerged over the past three decades as a new interdisciplinary science that offers novel approaches to the delivery of bioactive agents into the systemic circulation for a prolonged period at a predetermined rate. The choice of drug to be delivered, clinical needs, and drug pharmacokinetics are some of the important considerations in

the development of CR formulations, in addition to the relationship between the rates of drug release from the delivery system to the maximum achievable rate of drug absorption in to the systemic circulation. By achieving a predictable and reproducible bioactive agent release rate for extended period of time, CR formulations can achieved optimum therapeutic responses, prolonged efficacy, and also decreased toxicity. Therapeutic compounds with short half-life are excellent candidates for sustained-release preparations, since this can reduce dosage frequency.
Deflazacort(11β, 16β)-21-(acetyloxy)-11-hydroxy-2'-methyl- 5'H -pregna-1, 4-dieno[17,16-d] oxazole-3,20-dione, DEF) is a methyloxazoline derivative of prednisolone, that is used in rheumatoid arthritis, nephritic syndrome, organ transplantation rejection and juvenile chronic arthritis, among other diseases. It is a poorly water-soluble compound with an oral bioavailability of about 70 %, which exhibits low mineral corticoid activity and was promoted as a relatively bone-sparing glucocorticoid when compared with other glucocorticoids. The biological half life of Deflazacort is 1.1-1.9 hrs.

MATERIALS AND METHODS

Deflazacort (Aarthi Chemicals, Bombay), HPMC (Metolose 90 SH 100000 ShinEtsu, USA). Hydroxy Ethyl Cellulose (Natrosol 250 HHX Pharma Aqualon Hercules, USA). HPC (Klucel LF Pharma), Aqualon Hercules, USA. Povidone (Plasdone K29/32), ISP India Pvt Ltd., India Micro crystalline cellulose (Avicel PH 101), FMC Biopolymer, USA Purified Water, In-house , Magnesium Stearate, Feroo Industries, UK Aerosil, Degussa, Belgum.

5.3 PRE-FORMULATION STUDIES

Objective

The overall objective of preformulation testing is to generate information useful to the formulation in developing stable and bioavailable dosage forms.

Reasons for Preformulation Studies[6]

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first in the rational development of dosage forms

Scope

The use of preformulation parameters maximizes the chances in formulating an acceptable, safe efficacious and stable product.

Compatibility Studies[7]

Objective:

To find out suitable compatible excipients with selected drug for the formulation development For this study, based on the innovator data and literature data various excipients were selected for the study. Drug excipients mixtures were prepared and exposed to accelerated condition for selected time period and the excipients mixture were evaluated for any possible incompatibilities.

Procedure

The compatibilities were carried out to study the possible interactions between the active pharmaceutical ingredients and several inactive ingredients used in the formulations physical mixtures were kept in 40^{o}C / 75% RH and 60^{o}C in a 2ml glass vial in exposed condition for 1 month. excipients are mixed with drug.

At the interval of 2 weeks and 4 weeks the samples were withdrawn and analyzed for the following parameters at various temperatures and humidity conditions:

Table 1 Compatibility of Excipients

S. No	Drug+ Excipients	PARAMETER	Initial Value of Parameter	Condition			
				40°C+ 75% RH		60°C	
				2weeks	4weeks	2weeks	4weeks
1.	Deflazacort	Moisture content	2.38	3.68	4.42	1.69	1.54
		Assay	100.8%	99%	98.6%	100.9%	99.9%
2.	Deflazacort + HPMC	Moisture content	3.40	4.21	4.87	3.79	3.31
		Assay	100.7%	100.1%	99.8%	100.5%	100.2%
3.	Deflazacort + HEC	Moisture content	4.69	5.19	5.75	4.79	4.50
		Assay	99.8%	99.1%	98.2%	98.9%	98.1%
4.	Deflazacort + HPC	Moisture content	2.29	5.63	6.70	5.48	5.09
		Assay	101%	100.5%	99.4%	98.9%	98.6%
5.	Deflazacort + aerosil	Moisture content	5.62	5.84	6.33	6.63	6.52
		Assay	99.9%	99.2%	98.5%	98.3%	97.9%
6	Deflazacort + Magnesium stearate	Moisture content	1.55	4.48	4.63	1.57	0.82
		Assay	100%	101.7%	100.9%	99.8%	99.3%

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR was carried out between drug and the polymers physical mixtures. The FTIR was carried out on the Deflazacort and HPMC, HEC and HPC. The results obtained by the physical mixtures are compared with the standard graph.

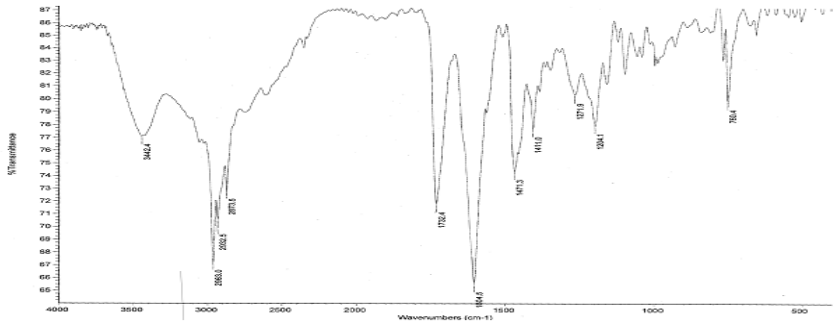


Fig No.1 FTIR OF DEFLAZACORT

Differential scanning colorimetry[8-10]

DSC was carried between drug and polymer physical mixtures in 1:1 ratio. The DSC was carried out on the Deflazacort and HPMC, HEC and HPC.

Preparation of controlled release tablets[11-13]

Controlled release tablets were prepared by wet granulation method. The composition of various formulations was shown in Table No 2. Formulation development of diffusion based controlled release matrix tablets of DEFLAZACORT using polymers such as HPMC K100M, ETHYLCELLULOSE 50CPS and HPC and passed through #30 mesh and Magnesium stearate

through #40 mesh and collect separately in polyethylene bag. Tablets were compressed at 287 mg weight on a 16-station rotary tablet punching machine (Cadmach Machinery pvt. Ltd,) with 8mm circular shaped deep concave punches plain on both twelve different formulae, having different concentrations were developed to evaluate the drug release and to study the effect of polymer concentration on drug release.

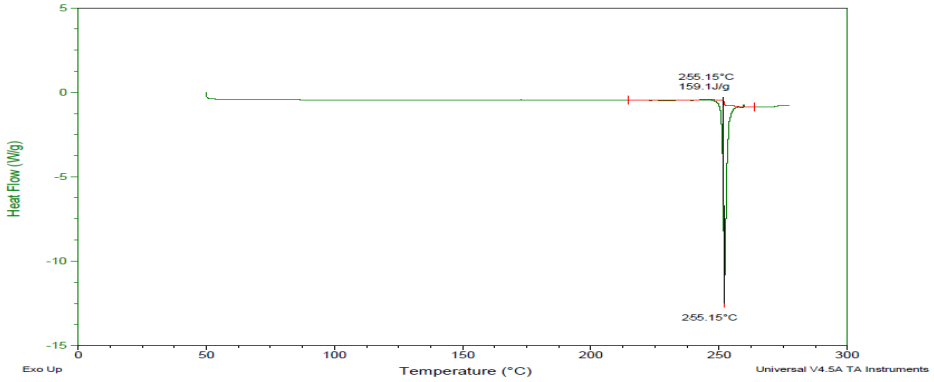


Fig No.2 DSC of pure deflazacort

Table 2: batches done for formulation development

Ingredients	Trail 1	Trail 2	Trail 3	Trail 4	Trail 5	Trail 6	Trail 7	Trail 8	Trail 9	Trail 10	Trail 11	Trail 12
Deflazacort	30	30	30	30	30	30	30	30	30	30	30	30
HPMC			75			10	25	10	25			112.5
HEC	75			65	50	65	50			112.5		
HPC		75		10	25			65	50		112.5	
Povidone	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
MCC PH 101	30	30	30	30	30	30	30	30	30	30.5	30.5	30.5
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Aerosil	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total tablet weight	143.5	143.5	143.5	143.5	143.5	143.5	143.5	143.5	143.5	181.5	181.5	181.5

NOTE: *All the quantities of Inactive Ingredients are taken on the basis of Trial and Error*

Evaluation of blend: [14-16]

The angle of repose was measured by using fixed funnel method, which indicates the flowability of the granules. Loose bulk density (LBD) and tapped bulk density (TBD) were measured using the formula: LBD= height of the powder / volume of the packing. TBD= weight of the powder / tapped volume of the packing. Compressibility index of the granules was determined by using the formula: CI (%) = [(TBD-LBD/TBD)] ×100.The physical properties of granules were shown in Table 3.

Evaluation of Tablets:

Thickness:

Thickness of the tablets was determined using a vernier calliper (For-bro engineers, Mumbai, India).

Weight Variation Test[17]
20 tablets of each formulation were weighed using an electronic balance (Sartorius electronic balance: Model CP-2245, Labtronic), and the test was performed according to the official method.

Hardness
Hardness generally measures the tablet crushing strength. Hardness of the tablets was determined by using a hardness testing apparatus (Monseto Type).

Friability[18]
The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai, India). Tablets of a known weight (W0) or a sample of tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1% w/w.10

$$\% \text{ Friability} = (W0\text{-}W)/ W0 \times 100$$

Tablet properties of the different formulations of Deflazacort controlled release core and coated matrix tablets were shown in Table No. 4.

In Vitro Release Studies[18,19]
In vitro dissolution studies were carried out using USP apparatus type II (at 50 rpm. Dissolution medium consisted of deairated water from 30mins to 12 hours maintained at 37°C ± 0.5°C. Drug release at different time intervals was measured by UV-visible spectrophotometer at 265 nm.

RESULTS AND DISCUSSION

FORMULATION DEVELOPMENT
In the present study, deflazacort was selected as a model drug in the design as controlled release tablet using HPMC as matrix forming polymer. Controlled release tablet of deflazacort was developed, in order to avoid fluctuations in the plasma drug concentration as well as for increasing bioavailability of deflazacort. Controlled release tablets each containing 30 mg of Deflazacort were prepared using three different polymers, HPMC, HPC, EC by wet Granulation method Formulation F1 and F10 were prepared by using HEC polymer. Drug release from these two formulations was found to be 97.68±0.09%, and 98.33±0.06 respectively. Formulation F2 and F11 were prepared by using HPC polymer.

Drug release from these two formulations was found to be 98.45±0.14%, and 99.84±0.02 respectively. Formulation F3 and F12 were prepared by using HPMC polymer. Drug release from these two formulations was found to be 98.09±0.13%, and 99.57±0.07 respectively. Formulation F4 and F5 were prepared by using HPC and HEC polymers. Drug release from these two formulations was found to be 99.86±0.11% and 99.17±0.12 respectively. Formulation F6 and F7 were prepared by using HPMC and HEC polymers. Drug release from these two formulations was found to be 99.53±0.14%, and 98.34±0.02 respectively. Formulation F8 and F9 were prepared by using HPMC and HPC polymers. Drug release from these two formulations was found to be 99.34±0.14%, and 98.60±0.09 respectively

Evaluation of tablet:

(a) Precompression parameters:

(i) Compressibility index:

Percent compressibility of powder mix was determined by Carr's compressibility index. The percent compressibility for all the twelve formulations lies within the range of 13.1 to 14.6. All formulations show good compressibility

(ii) Angle of repose:

Table No.3 shows the results obtained for angle of repose of all the formulations. The values were found to be in the range of $26.5^0$to 27.8^0 All formulations showed angle of repose within 31^0 which indicates good that showed little higher angle of repose above 30^0 indicating fair flow.

(iii) Bulk Density:

Both loose bulk density (LBD) and tapped bulk density results are shown in Table No.2. The loose bulk density and tapped bulk density for all the formulations varied from 0.52 gm/cm^3 to 0.59 gm/cm^3 and 0.60 gm/cm^3 to 0.69 gm/cm^3 respectively.

The values obtained lies within the acceptable range and not large differences found between loose bulk density and tapped bulk density. This result helps in calculating the % compressibility of the powder.

(iv) Hausner ratio:

Table No.3 shows the results obtained for Hausner ratio of all the formulations. The values were found to be in the range of 1.14to 1.16 All formulations showed that the powder was having free flow in nature.

Table 3: evaluation of pre compression parameters

S.No	Formulation code	Angle of repose	bulk density	Tapped bulk density	Hausners ratio	Compressibility index
1	F001	27.5	0.56	0.65	1.16	13.84
2	F002	26.8	0.54	0.63	1.16	14.28
3	F003	26.5	0.53	0.62	1.15	14.51
4	F004	27.8	0.52	0.60	1.15	13.5
5	F005	27.6	0.53	0.61	1.15	13.1
6	F006	26.9	0.58	0.63	1.14	14.6
7	F007	26.6	0.55	0.66	1.16	14.32
8	F008	27.4	0.51	0.60	1.15	13.55
9	F009	27.8	0.59	0.69	1.14	13.67
10	F010	27.6	0.55	0.62	1.15	14.1
11	F011	26.9	0.50	0.65	1.14	14.4
12	F012	27.1	0.54	0.69	1.16	13.98

(b) Post-compression Parameters:

1. Thickness test:

The thickness of the tablets from each formulation was measured by using vernier calliper by picking the three tablets randomly. The mean values are shown in Table No.4 the values are almost uniform were found in the range from 3.81 mm to 4.33mm.

2. Hardness Test:

Table No.4 shows results of hardness. Hardness test was performed by Monsanto tester. Hardness was maintained to be within 2.38 kg/cm^2 to 4.16 kg/cm^2, the hardness of all the

formulations were almost uniform and possess good mechanical strength with sufficient hardness.

3. Friability Test:

The study results are tabulated in Table No.4 was found well within the approved range (<1%) in all the formulation. Formulation F1 to F12 possesses good mechanical strength.

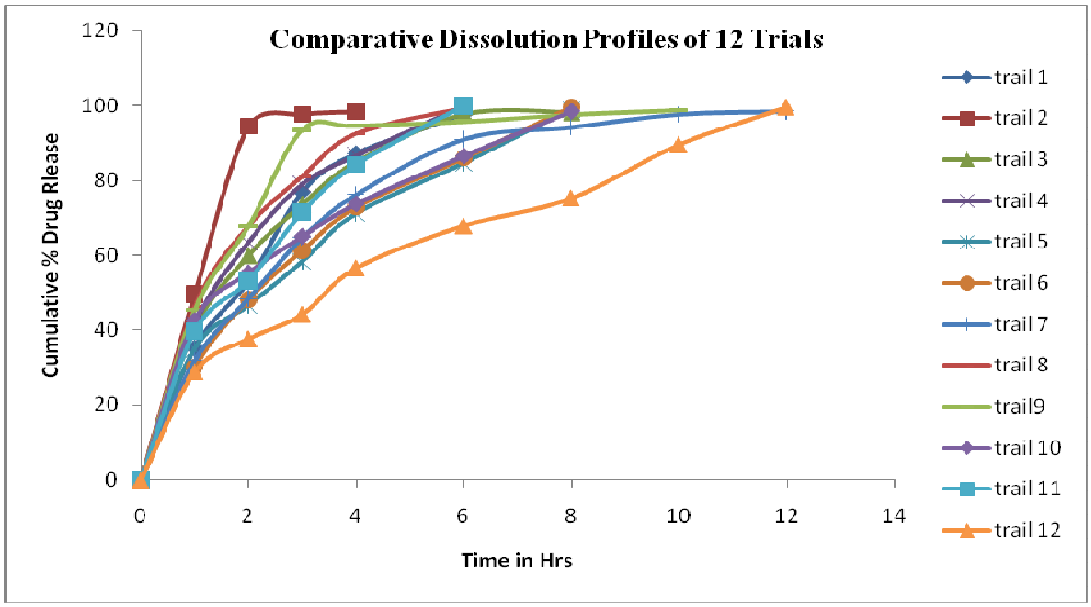
Table 2: evaluation of post compression parameters

S.No	Formulation code	Thickness		Hardness(N)		Friability (% w/w)	
		min	max	min	max	min	max
1	F001	3.89	4.11	67.8	80.1	0.52	0.98
2	F002	3.99	4.33	70.4	75.3	0.43	0.86
3	F003	3.87	4.12	61.3	78.6	0.48	0.92
4	F004	3.95	4.23	64.5	79.3	0.55	0.91
5	F005	3.95	4.14	69.9	77.6	0.41	0.89
6	F006	3.96	4.21	68.8	76.9	0.53	0.85
7	F007	3.88	4.28	72.4	79.9	0.42	0.88
8	F008	3.84	4.17	74.8	78.3	0.49	0.94
9	F009	3.87	4.10	71.2	76.4	0.44	0.91
10	F010	3.91	4.29	63.4	75,2	0.59	0.92
11	F011	3.93	4.20	69.5	76.5	0.57	0.90
12	F012	3.81	4.22	63.4	77.1	0.51	0.81

4. In vitro Dissolution Studies:

All the 12 formulations were subjected for *in vitro* dissolution studies using tablet dissolution tester USP XXIII. The samples were withdrawn at different time intervals and analyzed at 265nm. The results obtained in the *in vitro* drug release for the formulations F1 to F12are tabulated in Fig No.3

Fig No.3



Curve fitting analysis:

In order to establish the mechanism of drug release the experimental data was fitted to 5 popular exponential equations. The drug release was found to be followed zero order kinetics which was indicated slightly by higher "r" values of zero order release model (0.843 to 0.992) when compared to those of first order release model (0.581 to 0.930). The relative contribution of drug diffusion and matrix erosion to drug release was further confirmed by subjecting the dissolution data to Higuchi model and Erosion model. It was found that trial 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 followed diffusion mechanism (0.857 to 0.994) and Trial 1, 6, 7 followed Erosion mechanism as indicated by their respective "**r**" values was shown in Table No.5.

Table 5: Correlation Coeffient Values (R^2)

Trials	Zero order	First order	Higuchi	Erosion equation	Release exponent (n in peppas)
1	0.980	0.892	0.981	0.994	0.599
2	0.882	0.803	0.941	0.793	0.504
3	0.952	0.894	0.969	0.951	0.443
4	0.948	0.825	0.981	0.979	0.472
5	0.959	0.897	0.997	0.993	0.497
6	0.916	0.904	0.995	0.967	0.568
7	0.971	0.774	0.948	0.953	0.460
8	0.955	0.787	0.968	0.928	0.421
9	0.843	0.581	0.857	0.736	0.320
10	0.930	0.837	0.990	0.984	0.398
11	0.944	0.902	0.995	0.990	0.526
12	0.992	0.930	0.994	0.915	0.505

CONCLUSION

From the foregoing investigation it may be concluded that the release rate of drug was found to be followed zero order kinetics from the matrix tablets. The relative contribution of drug diffusion and matrix erosion to drug release was further confirmed by subjecting the dissolution data to Higuchi model and Erosion model. *In vitro* dissolution results showed that % of drug release was prolonged in formulation containing HPMC that is up to 12 hours when compared to other formulations. This indicates that the drug released from this formulation was effective up to 12 hours.

Acknowledgement

The authors are thankful to the Management, Aditya College Of Pharmacy, Surampalem for providing necessary facilities to carry out this work. And we are grateful to my parents to their encouragement and guidance.

REFERENCES

[1] N. G. Raghavendra Rao, *Der Pharmacia Sinica,* **2011**, *2 (2): 236-248.*
[2] Chien, Y. W. *Med. Prog. Techn.* **1989**, *15, 21-46.*
[3] Chein, Y. W. Novel Drug Delivery System, *Marcel Dekker Inc. New York.* **1992**, *14, 139-196.*
[4] Grass, G. M.; Robinson, J. R. Sustained and Controlled release drug delivery systems. In Modern Pharmaceutics. Banker, G. S.; Rhodes, C. T.; Eds.; *Marcel Dekker Inc: New York.* **1990**, *40, 2nd ed., 635-638.*

[5] Robinson, R.; Lee, V. H. Influence of Drug Properties and route of Drug Administration on the design of sustained and controlled release drug delivery system. In Controlled Drug Delivery Fundamentals and Applications. Robinson, R.; Lee, V. H.; Eds.; *Marcel Dekker Inc: New York,* **1995**, *29; 3rd ed.,. 3-35.*
[6] Lee, V. H. L.; Yang, J. J. Oral Drug Delivery. In Drug Delivery and Targeting. Hillery, A. M.; Llyod, A.W.; Swarbrick, *J.; Eds. Taylor and Francis: London and New York,* **2001**, *165-168.*
[7] Lordi, N. G. Sustained release dosage forms. In The Theory and Practice of Industrial Pharmacy. Lachman, L.; Lieberman, H. A.; Kanig J. L. Eds.; *Lea and Febiger: Philadelphia,* **1991**, *3rd ed.,. 430-435.*
[8] Hui, Ho- Wah; Robinson, J. R. Design and Fabrication of Oral controlled release drug delivery systems. In Controlled Drug Delivery Fundamentals and Applications. Robinson, R.; Lee, V. H.; Eds.; *Marcel Dekker Inc: New York,* **1995**, *29, 3rd ed., 373-378.*
[9] Shargel, L.; Wu- Pong, S.; Yu, A. B. Applied Biopharmaceutics and Pharmacokinetics. *Mc. Graw Hill,* **2005**, *5th ed., 515-520.*
[10] Aulton, M. E. Pharmaceutics The Science of Dosage Form Design. Churchill Livingstone. **2002**, 2nd ed., 414-418.
[11] Heller J, In: Robison J.R. and Lee VH Eds., *Controlled Drug Delivery: Fundamentals and Applications,* Marcel Decker, New York, **1987**., 179.
[12] Deepak Sahu, *Der Pharmacia Sinica*, **2010**, *1 (1): 48-57.*
[13] Makhija SN, Vavia PR. *AAPS PharmSciTech.* **2009** *june*
[14] J.Th.H. van Eupen, *International Journal of Pharmaceutics,* **2009**, *368, 146–153.*
[15] Charles B. Nemeroff a, Michael E. Thase b, On behalf of the EPIC 014 Study Group. *Journal of Psychiatric Research 41 (***2007***) 351–359.*
[16] Graham A. *Bioorganic & Medicinal Chemistry Letters 16 (***2006***) 2555–2558.*
[17] Michael C. Rowbothama,, Veeraindar Golib, Nadia R. Kunzc, Dean Lei. *Pain 110 (***2004***) 697–706.*
[18] Yoram sela. Extended release composition comprising as active compound venlafaxine hydrochloride. *United states patent application publication.* **2003**
[19] Sampad bhattachrya, rajesh kshrisagar , mayank joshi, sandeep pandita. Extended release formulation of venlafaxine hydrochloride. *United States patent application publication.* **2004**.