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Formulation and Evaluation of Escitalopram Solid dispersion using Biopolymer from *Cicer arietinum* Seeds

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Abstract: The current aim of our research work is to isolate a novel bio-dispersant from the seeds of *Cicer arietinum* and to formulate Escitalopram granules containing bio-dispersant. Bio-dispersant was isolated by treating the seeds of *Cicer arietinum* with double distilled water and treated with ethanol and the bio-dispersant was collected, further studied for physicochemical properties like color, odour, particle size, shape, solubility and IR spectral studies. Escitalopram granules were prepared using drug, lactose, bio-dispersant, bio-binder and other processing agents. Six different formulations were formulated with varying bio-dispersant concentration and bio-binder concentrations. The formulated granules were subjected for various evaluation parameters like particle size, flow properties, bulk density, tapped density, in-vitro release studies. In-vitro release studies were performed by filling the granules in the empty gelatin capsule. Our research results revealed that the isolated bio-dispersant exhibited a very promising significant dispersibility of granules within 1-5 seconds. 91 to 99.5% releases were observed in all the formulations. The formulated granules showed very good flow properties, dispersion time and release profile. Finally the smart conclusion was drawn out that the isolated biomaterial showed its in-built bio-dispersibility. It can serve as a novel bio-dispersant for the formulation of various dispersible granules and tablets.
Keywords: Escitalopram, *Cicer arietinum*, solid dispersion, bio-dispersibility.

Introduction and Experimental

Drug delivery science has gained greater significance over last few decades leading to advanced drug delivery technology platforms. Poor aqueous solubility of a number of drugs has been a major problem for the drug development which results in low bioavailability, high food effect and variable pharmacokinetic performance of many drug products.(1) The enhancement of the bioavailability of such poorly water soluble drugs remains one of the most challenging aspects of drug development. Over the years, formulation science has grown to embrace those poorly water soluble, highly effective therapeutic molecules and help them to develop into useful drugs.(1,2,3) Several techniques have been employed for improving the solubility of such compounds e.g. salt formation, prodrugs, polymorphs, conjugates, hydrates and solvates, liquisolids, nanograph, micronization, co-precipitation using antisolvent, adding surfactants. But ahead of all solid dispersion is the most promising method to formulators because of its ease of preparation, optimization and reproducibility.(1,2) Solid dispersion is defined as a

dispersion of one or more active ingredients in an inert carrier at solid state generally prepared by melting (fusion), solvent or melting solvent method in order to achieve enhanced dissolution state, sustained release drugs, altered solid state property, enhanced release of drugs from ointment and suppository bases and increase in solubility and stability. According to Chiou and Riegelman, "solid dispersion is a dispersion involving formulation of eutectic mixture of drugs with water soluble carriers by melting of their physical mixture".(3,4) Solid dispersion is a viable technique for enhancing solubility. (3) It has aroused great interest during past four decades and has emerged out as most viable and promising method to formulator. Escitalopram is the pure (S) enantiomer of racemic citalopram and is a selective serotonin reuptake inhibitor (SSRI). Escitalopram is used in the treatment of depression and anxiety. It is approved for the treatment of major depressive disorder and generalized anxiety disorder; other indications include social anxiety disorder, panic disorder and obsessive-compulsive disorder.(5)

Escitalopram acts by increasing intrasynaptic levels of the neurotransmitter serotonin by blocking the reuptake of the neurotransmitter into the neuron. Its half life is about 27-32 hours. It is metabolized in the liver, specially by the CYP3A4 and CYP2C19 after oral administration. Its bioavailability is 80% and protein binding is approximately 56%. It is poorly soluble in water so its absorption is less.(6-12) A number of polymers or carriers as Natural or synthetic hydrophilic colloids and Biocompatible polymer are used in the formulation of Solid Dispersion Technology asethylcellulose, hydroxyethylcellulose, Hydroxypropylcellulose, PLGA Albumin, Chitin ,Starch, Collagen, Chitosan, Dextrin . Most of these polymers are hydrophilic in nature, and after absorbing water they swell and form a viscous gel layer around the dosage form resulting into delayed/ sustained drug release. With the advancements in the field of Novel Drug Delivery Technology the use of bio-polymers for the preparation of solid dispersion for improving the solubility of poorly water soluble drug is encouraged.

The biopolymer derived from seeds of *Cicer arietinum* which contains different forms of glucose, sucrose, fructose, certain polysaccharides like starches, Gamma-galactan, para-galacto araban, betaine, adenine, inositol, saponin and acids like oxalic acid and citric acid. The biopolymers used for the preparation of solid dispersion improve the solubility of poorly water soluble.(13-20) The present work deals with preparation and evaluation of Escitalopram solid dispersion using biopolymers extracted from seeds of *Cicer arietinum* as bio-dispersant and bio-binder.

Materials and methods

Escitalopram was obtained as gift sample. Other materials used in study such as Lactose, Talc, ethanol etc were of suitable analytical grade. Quality *Cicer arietinum* seeds were bought from market.

Extraction of Biopolymers:

1 .Isolation of biopolymer 1 (BC A1):

Accurately weighed 250 g of Chana dal was soaked in 750 ml of distilled water in a 1 litre beaker and kept overnight in refrigerator for a period of 12 hours. Then the supernatant liquid was decanted over from it. The supernatant liquid obtained was cooled and then was subjected to centrifugation at 3000 rpm for 15 min . 250 ml of supernatant was taken in a beaker and treated with 500 ml of ethanol kept for 12 hours in refrigerator. The bio-material was separated by subjecting the mixture for centrifugation at a speed of 3000 rpm for 15 minutes. The bio-material was collected by decanting supernatant liquid and subjected for drying in desiccators for10 hours. The dried bio-material was passed through sieve #120.

2. Isolation of biopolymer 2 (BC A2):

250 g of Chana dal was soaked in water thrice of its volume in a 1 litre beaker and kept for 12 hours in refrigerator. Then the liquid was decanted over from it. The supernatant liquid was then subjected to centrifugation at 3000 rpm for 15 min. After that the supernatant liquid was subjected to evaporation till dryness. The bio-binder thus obtained was then passed trough sieve #120.

Preparation of Escitalopram bio-solid dispersion:

The objective of this study is to produce fast release solid dispersions of Escitalopram with improved therapeutic efficacy, immediate therapeutic effect by enhancing the solubility of this poorly water soluble drug.Two steps were followed for the preparation of solid dispersion:-

1.Preparation of solid dispersion mixture
2.Preparation of granules
3.Preparation of capsules containing solid dispersion granules

Table 1: Formula for different Formulations for 100 g each

Ingredients	FE 1	FE 2	FE 3	FE 4	FE 5	FE 6
Drug (mg)	20	20	20	20	20	20
Lactose (mg)	77.2	76.7	75.7	75.2	74.7	73.7
Binder (%)	2	2	2	4	4	4
Dispersant (mg)	0.5	1	2	0.5	1	2
Talc (mg)	0.3	0.3	0.3	0.3	0.3	0.3

1. Preparation of solid dispersion:

The solid dispersion of drug and BC A1 were prepared by dry mixing for different formulations as given in the **[Table 1].**

2. Preparation of granules containing solid dispersions:

The granules of solid dispersions were prepared by wet granulation technique. This technique involves three steps:-

1. Wet massing of powders.
2. Wet sizing.
3. Drying.

1. The different concentrations of binder solution of biopolymer BC A2 were prepared for preparing different formulations as given in the [Table 1]. Different proportions of solid dispersions, Talc and Lactose for various formulations as given in the table 1 were mixed by dry mixing in a pestle mortar. A wet mass of this was prepared with the binder solution so as to moisten rather than wet or pasty. The binder was blended in with the dry powders initially and then it was allowed for mixing continuously until a uniform dispersion was attained.
2. This wet mass thus prepared was allowed for wet screening by passing through the sieve #16. The procedure was repeated for each formulation. This wet screening converted the moist mass into coarse granules.
3. The prepared granules were dried in the tray dryer for 20 minutes at a temperature of 100º C to remove the solvent that was used in forming the granules and to reduce the moisture content to an optimum level of concentration within the granules. After drying, granules were screened again with sieve #80.

3. Preparation of capsules containing solid dispersion granules:

The empty capsule shells were weighed initially. 50 mg of the Escitalopram granules of different formulations were filled in the capsule shell manually and then the cap of the capsule shell was placed over the body of the capsule shell and were locked tightly and sealed. The filled capsules were subjected for reweighing.

Table 2: Physical Properties of Biopolymers

S.No.	Physical property	Bio-dispersant (BC A1)	Bio-binder (BC A2)
1.	Color	Reddish Brown	Yellowish Brown
2.	Odour	Characteristic	Characteristic
3.	Taste	Sweet	Characteristic
4.	Texture	Gummy like	Coarse powder
5.	Solubility	Soluble in water	Slightly soluble in water
6.	Melting Point	165-170°	Above 180°

Table 3: Dispersibility of various Binders

Binder	Dispersibility (s)
Acacia	5
Starch	4
Tragacanth	8
Bio-Binder(BC A2)	5
Bio-dispersant(BC A1)	3
No binder(plane water)	18

Evaluation Parameters:

The extracted biopolymers (BC A1 and BC A2) were then subjected to different evaluation parameters physical properties, chemical properties, IR spectroscopy and dispersibility. [Table 2] shows the physical properties of the isolated biopolymers.The bio-binder and the bio-dispersant were evaluated for IR spectral studies and the IR spectrum obtained are shown in [Figure 1] and [Figure 2]. The dispersibility of the granules of bio-binder and bio-dispersant were compared with granules prepared with other binding and dispersing agents and the results obtained are shown in [Table 3].All the prepared solid dispersion formulations were then subjected to different evaluation parameters as angle of repose, bulk density, tapped density and in-vitro dissolution studies. Flow properties of the prepared granules were assessed by determining the angle of repose of the powder. The prepared solid dispersion granules were also evaluated for bulk density and tapped density.

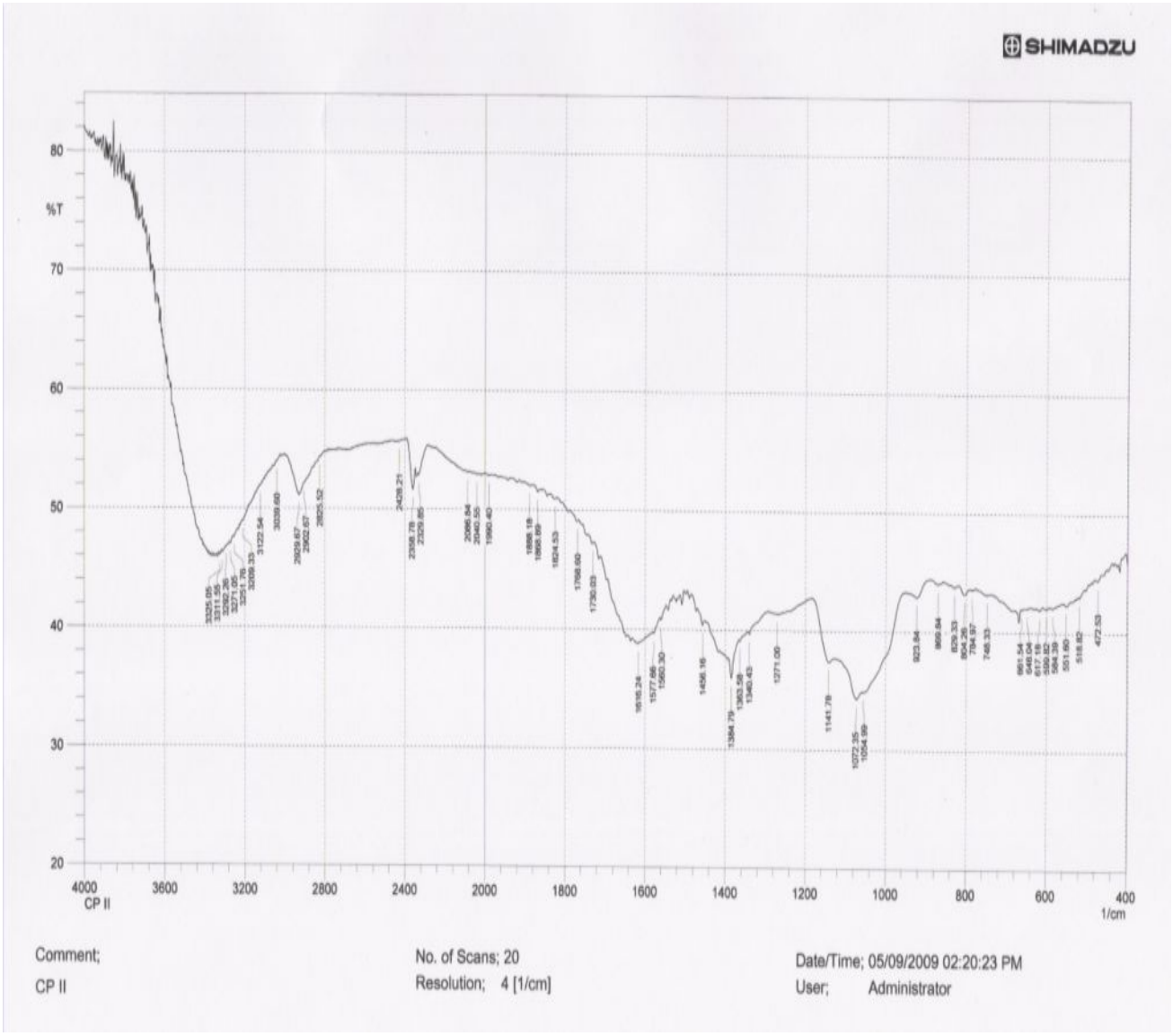

Figure 1: IR spectrum of bio-polymer BC A2

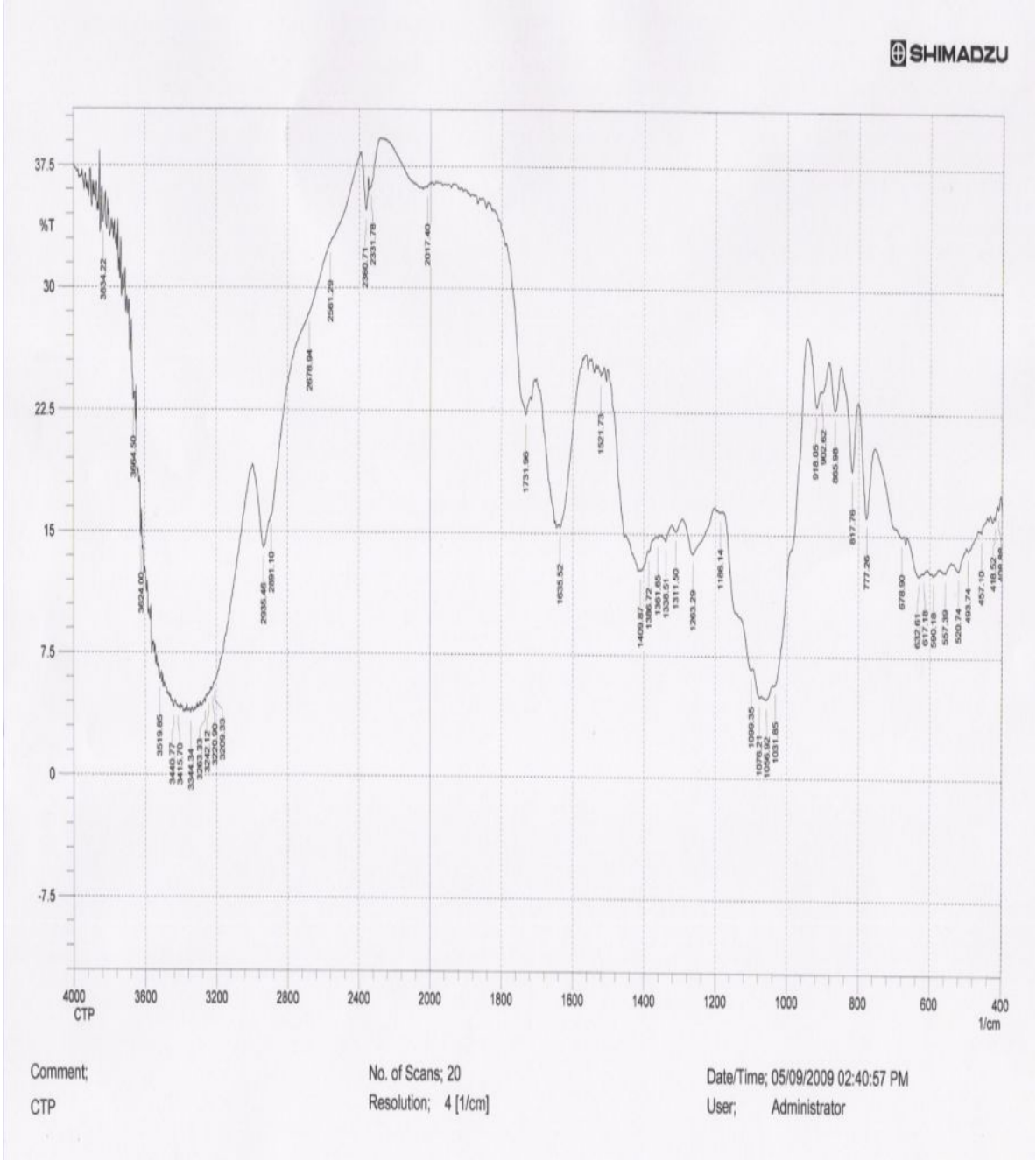

Figure 2: IR spectrum of bio-polymer BC A1

In vitro dissolution studies were performed by USP dissolution apparatus type II using buffer pH 1.2 at the temperature 37 ± 0.5. One capsule containing 10 mg of the drug was transferred into the dissolution basket containing 300 ml of pH 1.2 buffer.5 ml of samples were withdrawn at 2 min, 4min, 8min, 12min, 16min, 20min, 25min and 30 min .5 ml of fresh buffer was replace after each withdrawal. The withdrawn samples were diluted suitably, filtered & the absorbance was measured using UV spectrophotometer (shimadzu) at λ_{max} 275nm.The % Release of drug from the formulation was determined. The T50% and T80% were calculated for each formulation by extrapolation.

Table 4: Angle of Repose, Bulk Density and Tapped Density of various Formulations

Formulation	Angle of repose (°)	Bulk Density(g/ml)	Tapped Density(g/ml)
FE1	25.56	0.446	0.52
FE2	14.47	0.457	0.594
FE3	16.50	0.399	0.487
FE4	23.05	0.5	0.542
FE5	27.55	0.466	0.505
FE6	16.26	0.476	0.605

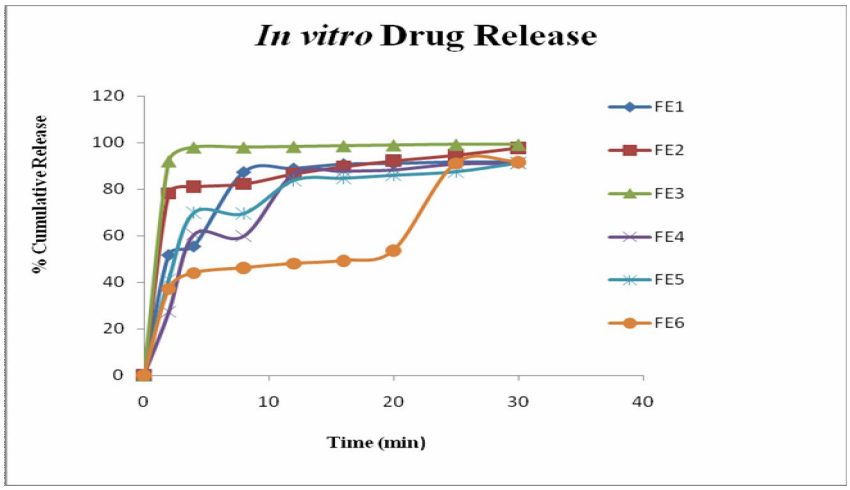

Figure 3: *In vitro* drug release from Escitalopram Solid dispersions using pH 1.2

Results and Discussions

The bio-dispersant (BC A1) and bio-binder (BC A2) were isolated successfully. The extracted bio-dispersant and bio-binder were evaluated for their physical characteristics, Chemical characteristics and IR spectral studies. The isolated bio-binder and bio-dispersant were used for the various formulations of solid dispersions of Escitalopram. The granules of solid dispersions prepared were found out to be having good flow properties as the angle of repose was found out to be less than 20°.The granules of lactose prepared using bio-binder & bio-dispersant were found to have good dispersibility as compared to the granules of lactose prepared with other binding & dispersing agents as shown in [Table 3]. Different formulations were evaluated for Flow properties, Bulk Density, Tapped density and the results obtained are shown in [Table 4]. The formulations were subjected to *in vitro* dissolution studies and the results obtained are as shown in [Figure 3]. Based on the different evaluation parameters and comparing the T50 and T80 of all the formulations FE 3 was found out to be the best formulation as it released the 90 % drug in 2 minutes. Thus the biopolymers isolated from the seeds of *Cicer arietinum* were found to be safe, biodegradable and effective for the formulations of bio-solid dispersions to enhance the solubility of poorly water soluble drugs as Escitalopram.

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References

1. Sandhu, Harpreet, Theoretical and practical considerations governing the selection of technology for improving the bioavailability of poorly water soluble drugs, Sience Abstracts, 60th IPC Delhi.

2. Karanth H, Shenoy V.S. and Murthy R.R., Industrially feasible approaches in manufacturing of solid dispersions: A Technical Report, AAPS Pharm Sci Tech.2006; 7(4): Article 87. DOI:10.1208 /pt070487.

3.Chaudhary P.D. et al. Current trends in solid dispersion techniques.

http://www.pharmainfo.net/reviews/current-trends-solid-solid-dispersion-techniques.

4.Chio W.L. and Rielman S., Pharmaceutical application of solid dispersion system, J.Pharm.Sci.1971;60, 1281-1302.

5.Andrea Cipriani, Toshiaki A Furukawa, Georgia Salanti and John R Geddes, Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis, The Lancet , Published Online, January 29, 2009, DOI:10.1016/S0140-6736(09)60046-5.

6. Zoloft, Lexapro the Best of Newer Antidepressants, HealthDay News, Washington Post, January 29, 2009.

7."2000 Annual Report. p 28 and 33" (PDF). Lundbeck. 2000. http://www.materials. lundbeck.com /lundbeck/82/fullpdf/1.pdf. Retrieved on 2007-04-07.

8. "New drugs from old. Presented at the Medical Journal Club, Morriston Hospital by Scott Pegler, Pharmacist at the National Health Service (UK) on November 20, 2006" (PPT). http://www.pharmedout.org/Pegler_New_Drugs_From_Old_Nov2006.ppt. Ret35)

9. "Cipralex". Lundbeck. http://www.lundbeck.com/products/our_products/cipralex/default.asp. Retrieved on 2008-01-03.

10. Burke W.J. and Kratochvil C.J., Stereoisomers in Psychiatry: The Case of Escitalopram(PDF). *Prim Care Companion J Clin Psychiatry.*2002; 4 (1): 20–24. PMID 15014731. http://www.psychiatrist. com/pcc/ pccpdf/v04n01/v04n0107.pdf.

11. Sanchez C, Bogeso K.P., Ebert B, Reines E.H. and Braestrup C, Escitalopram versus citalopram: the surprising role of the R-enantiomer. *Psychopharmacology (Berl.)*. 2004;174 (2): 163–76. doi:10.1007/s00213-004-1865-z. PMID 15160261.

12. Chen F, Larsen M.B., Sánchez C and Wiborg O, The S-enantiomer of R,S-citalopram, increases inhibitor binding to the human serotonin transporter by an allosteric mechanism. Comparison with other serotonin transporter inhibitors, *European Neuro psychopharmacology.*2005; 15 (2): 193–198. doi:10. 1016/j.euroneuro.2004.08.008.PMID 15695064.

13. Pigott T.A., Prakash A, Arnold L.M., Aaronson S.T., Mallinckrodt C.H. and Wohlreich M.M., Duloxetine versus escitalopram and placebo: an 8-month, double-blind trial in patients with major depressive disorder, *Curr Med Res Opin*. 2007;23: 1303. doi:10.1185/030079907X188107. PMID 17559729.

14. Davidson J.R., Bose A and Wang Q, Safety and efficacy of escitalopram in the long-term treatment of generalized anxiety disorder, *J Clin Psychiatry*. 2005;66 (11): 1441–6. PMID 16420082.

15. Kasper S, Lemming O.M. and de Swart H, Escitalopram in the long-term treatment of major depressive disorder in elderly patients, *Neuropsychobiology*. 2006;54 (3): 152–9. doi:10.1159/000098650. PMID 17230032.

16. Guerdjikova, Anna I, Susan L. McElroy, Renu Kotwal, Jeffrey A. Welge, Erik Nelson, Katie Lake, David D' Alessio, Paul E. Keck Jr and James I. Hudson, High-dose escitalopram in the treatment of binge-eating disorder with obesity: a placebo-controlled monotherapy trial, *Human Psychopharmacology: Clinical and Experimental*. 2008;23 (1): 1–11. doi:10.1002/hup.899. PMID 18058852.

17. Pedersen A.G., Escitalopram and suicidality in adult depression and anxiety, *International Clinical Psychopharmacology.* 2005; 20 (3): 139–143. doi:10.1097/00004850-200505000-00003. PMID 15812263.

18. Cavalier M, Benoit J.P. and Thies C, The formulation and characterization of hydrocortisone loaded poly (D,Llactide) microspheres, J. Pharm. Pharmacol.1986; 38: 249–253.

19. Juni K, Ogata J, Nakano M, Ichihara T, Mori K and Akagi M, Preparation and evaluation in vitro and in vivo of poly (lactic acid) microspheres containing doxorubicin, Chem. Pharm. Bull.1985; 33: 313–318.

20. Nixon J.R., Khalil A.H. and Carles J.E., Phase relationship in the simple coacervating system isoelectric gelatine:ethanol:water, J. Pharm. Pharmacol.1966; 18: 409–416.

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