SSRI Antidepressants: Focus on Escitalopram

by Fiona Geiser, Ph.D., CPhT

Escitalopram is an antidepressant from the class called Selective Serotonin Reuptake Inhibitors (SSRI’s). SSRI’s were among the first pharmaceutical products commercialized as single enantiomers following a 1992 United States Food and Drug Administration (FDA) Policy Statement. The directive required a thorough investigation of the biological and toxicological properties of single enantiomers. Dr. Geiser explains the research role she played to bring escitalopram and other new drugs to market.

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This article focuses on Escitalopram, a SSRI antidepressant, marketed in the United States by Forest Laboratories and elsewhere by Lundbeck. Research on the development of escitalopram began in the summer of 1997, resulting in a new drug application submitted to the US Food and Drug Administration in March 2001. The FDA approved escitalopram for major depression in August 2002 and for generalized anxiety disorder in December 2003. Although commercialization of a pharmaceutical product requires an extensive team effort, I had the opportunity to be the chemical researcher in the summer of 1997 who discovered the route by which escitalopram was eventually manufactured. The short time (3.5 years) for the development of escitalopram was due to the extensive experience of Forest and Lundbeck with citalopram, also approved for depression, and sold in the United States beginning in 1998.

Citalopram is not escitalopram. Citalopram is a 50:50 mixture of two, nearly identical, chemicals: S-citalopram (escitalopram) and its enantiomer, R-citalopram. Enantiomers are similar to our right and left hands. Although they appear identical, it is impossible to overlay our hands on top of each other. In other words, our hands are mirror images of each other. Escitalopram is the active enantiomer that treats depression. R-citalopram exhibits very little antidepressant properties, and worse, its presence cancels out the benefits of escitalopram. Removing the inactive, antagonistic R-citalopram made it possible to significantly lower the effective dose of escitalopram and it also improved the onset of action.

In 1980, most pharmaceutical products were clinically tested and introduced as 50:50 mixtures of enantiomers (called racemic mixtures). In 1992, the FDA issued a policy statement that racemic mixtures of new drugs could not be introduced without thorough investigation of the biological and toxicological properties of the individual enantiomers. Today, all new drug candidates are tested from the earliest stages as single enantiomers, if the chemical has a “chiral” site. What is a chiral site? Usually, a chiral site is a carbon on a molecule that contains 4 completely different attachments, such as circled in the red box for escitalopram (Fig. 1). Like our hands, it is impossible to overlay two enantiomers, although enantiomers exhibit identical chemical properties. As the story of escitalopram illustrates, enantiomers rarely exhibit identical biological properties.

An episode of major depression is defined as a depressed mood, or a loss of interest or pleasure, on a daily basis for a minimum of two weeks. Major depression will afflict about 15% of the population at some point in their lives, and is twice as common in women than in men. Diagnosis by a psychiatrist requires that certain criteria are met that may include: (1) markedly decreased interest in most daily activities; (2) recurrent thoughts of death and suicidal ideation; (3) physical fatigue and loss of energy; (4) a sense of worthlessness; (5) insomnia; (6) diminished ability to think or indecisiveness; (7) significant weight loss when not dieting; (8) psychomotor agitation or retardation nearly every day that is observable by others. About 60-70% of patients respond to an antidepressant, if it is given in a sufficient dose for 6 to 8 weeks. Although the biological cause of major depression is not understood, a class of drugs, called SSRI’s (selective serotonin reuptake inhibitors), was introduced to the United States in 1987 by commercialization of the racemic mixture, fluoxetine. Key advantages of SSRI antidepressants, compared to tricyclic antidepressants (TCA), were reduced side effects and improved safety. Whereas lethal overdose on a SSRI antidepressant is rare, suicidal patients require strict control of access to TCA medication in order to prevent lethal overdose.
Two other SSRI’s, sertraline and paroxetine, were commercialized in the United States in 1992 and 1993, respectively. Both sertraline and paroxetine have two chiral sites as shown in Fig. 2. When two chiral sites are present on a molecule, there are four potential enantiomers, sort of like two hands and two feet. If only one of the four enantiomers is biologically active, the resulting product consists of 75% impurities, an unacceptable situation. For this reason, chemists designed unique synthetic routes for the single enantiomers of sertraline and paroxetine. Since the development of such synthetic routes is a time-consuming process, most pharmaceutical researchers desired a rapid means of obtaining sufficient quantities of single enantiomers for initial biological studies. Beginning in 1995, my job was to develop those methods.

Pharmaceutical investigators from around the world sent me racemic mixtures of commercial as well as developmental candidates with the request to discover methods by which the enantiomers could be separated (resolved) using chromatography. The enantiomers for many pharmaceutical products had never been resolved and investigators needed to do basic studies in order to determine which enantiomer was the most biologically active. I typically developed a method in a day or two and then transferred the method to a chemical engineer who scaled up the method in order to isolate multigram quantities of the single enantiomers. The research investigators conducted initial studies and usually identified the “target” enantiomer, requesting additional scale up to kilogram or larger quantities.

By the summer of 1997, my toolbox had evolved so that I had approaches to solve particularly difficult problems, such as chemical instability. The difference between my chromatography methods and synthetic methods is that I was swamped with samples!! I was the only analyst in the laboratory and I needed to develop automated “screening” procedures that could evaluate 10 to 20 samples overnight. The chromatography equipment operated unattended overnight and I sorted through the results the next morning. Promising methods were then quickly fine tuned (optimized).

A synthetic chemist is required to develop a procedure customized to the structure of the compound. In contrast, I separated a racemic mixture at some point in the synthetic route. My separation procedures were generic with minimal concern for the structure of the compound. Over a decade later, these same generic “screening” techniques are still considered the fastest way to isolate single enantiomers. Developing a commercial process for escitalopram proceeded quickly using these screening methods, and clinical trials were soon underway in Europe. Although investigators were initially surprised by the clinical advantages of removing the inactive R-enantiomer of citalopram, current research studies are making progress in understanding the neurological basis for the differences.

The pharmaceutical industry and the FDA subsequently supported the new paradigm that pharmaceutical products needed to be developed and commercialized as single enantiomers. Racemic mixtures of commercial products, for which patents had expired, were reintroduced as the single, active enantiomers. An example of chiral chromatography equipment used today in the screening stage is shown in Fig. 3. Typical chiral manufacturing equipment is shown in Fig. 4. Although the equipment looks complex, the basic technology is shown in Figs. 5-8. In Fig. 5, a solvent, such as ethanol or methanol, is pumped through a metal column containing an adsorbent that looks a lot like flour before it is packed into the column. The sample of a racemic mixture is injected onto the column. The enantiomers separate (partition) on the adsorbent. Fig. 6 is a picture of the two enantiomers as they come off (elute) from the column. F1 stands for fraction 1, the first enantiomer, and F2 stands for fraction 2, the second enantiomer. The fractions are collected in separate containers and analyzed separately as shown in Fig. 7. The chromatography method is scaled up simply by increasing the size of the column and by increasing the flow rate of the solvent (eluent). As the demand grew for very large
quantities of single enantiomers, sophisticated engineering equipment was developed so that the chromatography process could be operated continuously and automatically as shown in Fig. 4. The most important component of the technology is the adsorbent used in the columns, called the chiral stationary phase (CSP’s). Finding the most effective CSP is done in the earliest stages of method development using a piece of equipment that looks like an octopus (Fig. 8). This was the type of equipment that I used in 1995 so that many columns could be tested overnight without requiring my presence to change the columns. Also, using this type of automated equipment, I could operate three or four chromatographs at the same time. Fortunately, reliable computer software was available at that time in order to store the results for review later on.

In summary, I am grateful to have had the opportunity to develop technology that has helped people. Nearly every week, friends will tell me how escitalopram helped lift their cloud of depression. When I was studying for my Ph.D., my primary goal was to learn enough so that I could contribute meaningfully to the health care industry. The old cliché is true: you have to be at the right place at the right time with the right skill set in order to make a difference. Also, more importantly, society must have the magic combination of the right technology and the mind set to change the status quo.
Additional Reading


Chiral Site for Escitalopram

Figure 1. Chiral Site for Escitalopram shown in the red box. Chiral sites usually have four different R groups and the enantiomers are mirror images of each other.
Figure 2. Both Sertraline and Paroxetine have two chiral sites. Can you identify the chiral sites? Both SSRI’s were commercialized as single enantiomers.
Figure 3. Typical chiral chromatography equipment used to discover a method to separate enantiomers from a racemic mixture.
Figure 4. Production-scale chromatography equipment operates continuously under computerized control.
Figure 5. A simplified schematic of chiral chromatography. Solvent (eluent) is pumped from left to right through a column packed with an absorbent. Sample is injected and enantiomers are resolved (separated) on the column. Enantiomers individually elute from the column and are detected in an ultraviolet detector. The resulting chromatogram is shown in Figure 6.
Figure 6. The above chromatogram is a visual picture of the events described in Figure 5. F1 is the first enantiomer eluting from the column. F2 is the second enantiomer eluting from the column. The enantiomers are collected in separate containers and analyzed separately as shown in Figure 7.
Figure 7. Each of the enantiomers collected in Figure 6 are analyzed separately to determine enantiomeric purity.
Figure 8. The most important component of a chiral chromatography method is the chiral stationary phase (CSP) packed inside the metal columns. Different chiral columns are tested automatically using a bank of columns. Automated equipment makes it possible for a single analyst to simultaneously operate 3 or 4 instruments. Results are stored in a computer for later review.