



## Magnetic Mirtazapine Loaded Poly(propylene glycol) bis(2aminopropylether) (PPG-NH<sub>2</sub>, MW<sub>2000</sub>) Nanocarriers for Controlled Drug Release

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### Abstract

Mirtazapine is an antidepressant that was introduced in 1996 for the treatment of moderate and severe depression. Mirtazapine is the only tetracyclic antidepressant that is approved by the Food and Drug Administration to treat depression. Mirtazapine is devoid of most side effects but has antihistamine side effects of drowsiness and weight gain. Its bioavailability is only fifty percent. The low bioavailability and side effects can be improved by altering the pharmacokinetic profile of the drug by controlling the release of the drug. The slow release of the drug will reduce the harmful affect it has on the cells decreasing the side effects, as well as the loading of the drug in the nanocarrier will allow for a longer residence time in the body before it is removed by the gastrointestinal tract.

In this research paper the pharmacokinetic profile of Mirtazapine will be altered by surrounding the drug with a biodegradable polymer called poly(propylene glycol) bis(2-aminopropylether) (PPG-NH<sub>2</sub>, MW<sub>2000</sub>) chains. This profile will be done at different polymer concentrations, drug concentrations and solubilizer concentration to see how this will affect the release of the drug.

In this research project it was found that using a lower concentration of poly(propylene glycol) bis(2-aminopropylether) (PPG-NH<sub>2</sub>, MW<sub>2000</sub>) chains of 0.5 g/mL led to a slower release in comparison to the other polymer concentrations with an encapsulation of 10 mg of Mirtazapine. When the drug weight was increased but the polymer concentration stayed the same (0.95 g/mL) the release rate increased with drug concentration. Also when the stabilizer concentration was increased, but the polymer concentration and drug concentration remained the same (0.95 g/mL and 10 mg respectively) the release rate increased. Therefore in order to allow for a slower release rate one should use the lower polymer concentration of 0.95 g/mL, with the lower concentration of stabilizer. This will allow for a slower release of the drug Mirtazapine which will lower the side effects and increase the bioavailability percentage.

**Keywords:** Nanomedicine; Nanotechnology; Pharmaceutical; Engineering; Controlled release

### Nomenclature

PBS: Phosphate Buffer Solution

PPG-NH<sub>2</sub>: Poly(propylene glycol) bis(2-aminopropylether)

BCD: Beta Cyclodextrin

MRZ: Mirtazapine

### Objective

The objective of this report is to improve the bioavailability and decrease the side effects of MTZ in the human body. This will be done by incorporating MTZ in a PPG-NH<sub>2</sub> nanocarrier which will allow for controlled drug release. Controlled drug release allows for a certain amount of drug to be released from the nanocarrier reducing the amount of drug interacting with cells. Also since the drug will be incorporated in a biodegradable nanocarrier this will allow a reduction in uptake of the nanocarriers by the gastrointestinal tract.

### Introduction

Mirtazapine (MTZ) is an antidepressant introduced by Organon International in 1996 which was used to treat moderate to severe depression. MTZ has a tetracyclic chemical structure and is an antidepressant that has been approved by the Food and Drug Administration to treat depression. MTZ is unique because it is virtually devoid of anticholinergic effects, serotonin-related side effects and adrenergic side effects [1]. However side effects such as drowsiness and weight gain are prominent [2]. Mirtazapine has a bioavailability of fifty percent [3].

This bioavailability can be enhanced by controlling the release of the drug from a formulation. Therefore biodegradable nanocarriers were created to prolong the release of the drug in systemic circulation. The antihistaminic side effects can also be decreased by decreasing the amount of dose that can be used for treatment [4]. This can also be achieved by using nanocarriers. Biodegradable and injectable microspheres have been studied in the past thirty years, they can significantly prolong the duration of the drug which are metabolized in the gastrointestinal tract. The total dose of the drug and some of the adverse reactions can be reduced because it allows for steady plasma concentrations [4]. Biodegradable polymers are therefore becoming more important for the development of sustained release drug delivery systems and implantable biomaterials [3]. The common biodegradable polymers used are polylactide co-glycolide. However in this project magnetic drug loaded nanoparticles were created using poly(propylene glycol) bis(2-aminopropylether) (PPG-NH<sub>2</sub>) as the biodegradable polymer and Iron oxide magnetic nanoparticles. Magnetic nanoparticles allow for the drug encapsulated nanocarriers to be transferred to the place of interest using a magnet, this leads to greater therapeutic efficacy. In this report there

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will be a comparison of the cumulative release of Mirtazapine (MTZ) from polymers of different concentrations, MTZ weight and Betacyclodextrin (BCD) concentration. This information will then be used to determine which polymer concentration and BCD concentration leads to the optimal drug. The encapsulation efficiency and drug loading of the nanocarrier can be calculated using these equations below:

$$\text{Entrapment Efficiency: } \frac{\text{Actual weight of drug Loaded in Nanoparticle} * 100\%}{\text{Theoretical weight of drug loaded in nanoparticle}}$$

The cumulative release of the drug was calculated using this equation:

$$\frac{\text{Concentration of drug released into PBS solution} * 100\%}{\text{Concentration of total drug loaded}}$$

## Materials

The materials used in this lab are Mirtazapine, Beta Cyclodextrin and ferrous sulphate heptahydrate, PPG-NH<sub>2</sub>.

- ▶ PPG-NH<sub>2</sub> is a biodegradable polymer that is starting to be used as a nanocarrier in drug delivery, allowing for a slow release of the drug.
- ▶ Mirtazapine, as described before is a drug that treats depression. It has a low bioavailability of around 50% and side effects such as weight gain.
- ▶ BetaCyclodextrin, is a stabilizer. It has a hydrophilic exterior and a hydrophobic core. It forms a complex around hydrophobic drugs providing stability. It also allows for an increase in the bioavailability of the drug. This occurs because betacyclodextrin and drug are released together, and the complex does not allow it to be recognized as something to be removed by the body along for greater residence time in the body.
- ▶ Ferrous sulphate heptahydrate creates Iron oxide nanoparticles when Iron ferrous sulphate heptahydrate in water had Ammonium oxide dripped into it while stirring occurred creating iron oxide. Incorporating this technique into the creating of MRZ loaded PPG-NH<sub>2</sub> magnetic nanoparticles allowed for the creation of controlled release magnetic particles.

## Methodologies

### Preparation of magnetic MTZ nanospheres

The magnetic MTZ nanoparticles were created by combining PPG-NH<sub>2</sub>, water, ferrous sulphate heptahydrate and stirring this mixture at fifty degrees Celsius. Betacyclodextrin with ammonium hydroxide was added drop wise to this mixture while increasing the temperature to one hundred degrees Celsius. The magnetic nanoparticles were then washed with ethanol/water. After nanoparticles were mixed with mirtazapine and water, forming mirtazapine magnetic nanocarriers. The supernatant was then removed and entrapment efficiency was calculated.

**Characterization of nanocarriers:** The supernatant was removed and the drug content was determined spectrophotometric ally at 290 nm.

### Equipment and Software Used to Analyze Data

**Zeta Particle Sizer:** The Zetasizer 3000 HS<sub>A</sub> (Malvern Instruments) laser diffraction particle size analyser delivers rapid and accurate particle sizes for wet and dry dispersions. It measures over the nanometer to millimeter particle size range. The Zetasizer was used to find the mean diameters of the individual particles Nanoparticle suspensions of 1.0 mg/L were prepared and diluted by a factor of 45

to obtain homogenous suspensions of nanoparticles. Three runs were carried out per sample in order to get a standard deviation.

**UV-Vis Spectroscopy:** The UV Spectroscopy was used to determine the concentration of the release of Mirtazapine using UV-visible spectroscopy based on the absorbance at 290 nm. This was completed when 1mg of mirtazapine loaded particles were dispersed in 10 mL of phosphate buffered saline solution. At predetermined intervals the particles were separated using a magnet and the liquid was collected and replaced with fresh buffer solution. The concentration of the mirtazapine in the liquid was measured using the UV-visible spectroscopy.

**In vitro release:** For *in vitro* release, weighed microspheres containing a specific amount of MTZ were suspended in Phosphate buffer solution pH 7.4. The drug release was assessed intermittently, and 2 ml of the media were removed, filtered and the amount of MTZ released in the buffer solution was quantified by UV spectrophotometer at 290 nm.

## Results

Table 1 shows entrapment efficiency, particle size, PDI.

- [1] 0.95 mg/mL + 1.5 mmol BCD + 10 mg MRZ
- [2] 0.95 mg/mL + 0.5 mmol BCD + 10 mg MRZ
- [3] 2.8 mg/mL+ 1.5 mmol BCD + 10 mg MRZ
- [4] 1.9 mg/mL+ 1 mmolBCD + 10 mg MRZ
- [5] 0.95 mg/mL+ 1 mmolBCD +10 mg MRZ
- [6] 0.95 mg/mL + 1 mmol BCD +20 mg MRZ
- [7] 0.95 mg/mL + 1 mmol BCD + 15 mg MRZ

Figure 1 shows Mirtazapine Standard Curve.

Figure 2 shows the effect of polymer concentration on Cumulative drug release.

Figure 3 shows the effect of the weight of drug on Cumulative drug release.

Figure 4 shows the effect of the amount of BCD on Cumulative drug release.

## Discussion

In this lab one created magnetic nanoparticles with MRZ loaded drugs. From the data in Table 1 and the data from Appendix 1.1 one can see that the entrapment efficiencies obtained were similar regardless of the concentration of polymer, amount of drug or concentration of BCD. The entrapment efficiency was around 97 percent.

Through *in vitro* studies one measured the cumulative concentration vs. time of the drug in phosphate buffer solution (PBS).

S.no	Entrapment Efficiency (%)	Particle Size(nm)	PDI
1	97.2348 ± 0.091	13.403	0.356
2	97.8192 ± 0	13.143	0.312
3	98.0205 ± 0.499	13.992	0.295
4	97.8249	11.097	0.125
5	98.7190 ± 0.0554	9.173	0.213
6	98.7395 ± 0.00501	15.7	0.321
7	98.8543	16.5	0.238

Table 1: Entrapment efficiency, particle size, PDI.

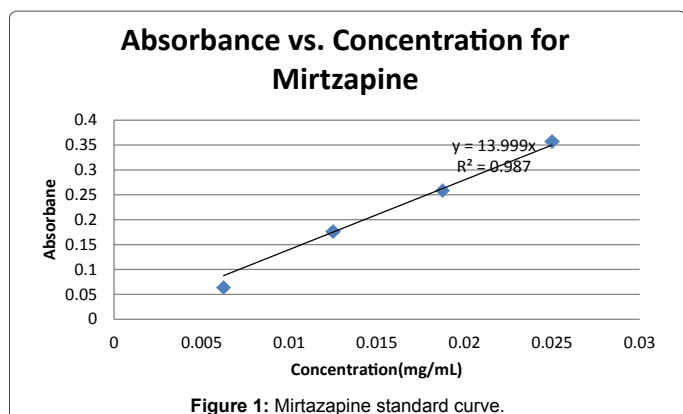
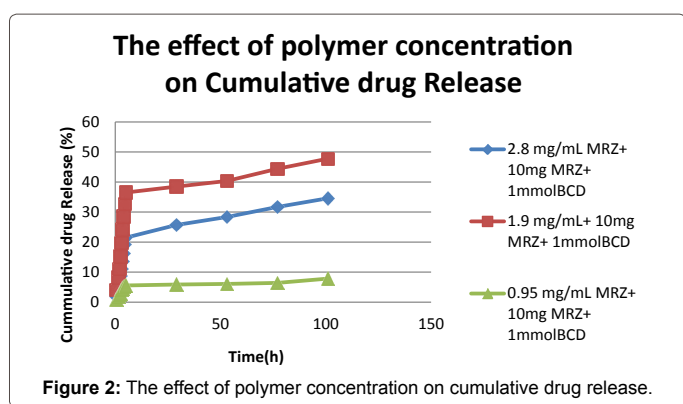


Figure 1 and the data in Appendix 1.2 were used to determine the concentration of each drug variation at different time intervals. The cumulative concentration vs. time graph was completed by finding the absorbance for each variation of drug at different time intervals. Then the concentration of each drug was determined using Figure 1 and the results can be seen in Appendix 1.3. The cumulative concentration was then calculated and the values can be seen in Appendix 1.4, Appendix 1.5 and Appendix 1.6. The resulting data was graphed in Figures 2-4.

As one can see from figure two, as the polymer concentration increased the rate of drug dissolution increased. However when one compares a concentration of 1.94 mmol/mL to 2.84 mmol/mL the dissolution rate is higher than 0.95 mmol/mL but the 1.94 mmol/mL concentration has a higher dissolution rate than the 2.84 mmol/mL concentration. This could be due to the amount of BCD in the polymer. BCD allows for a faster dissolution of the drug out of the nanocarrier [1], however it has also been known to cause a slower dissolution rate [1] because it takes a longer time for BCD to diffuse through the matrix of the polymer depending on the concentration of the polymer. As the concentration, of the polymer increases the ability for BCD to become entrapped in the matrix increases.



In Figure 3 it is shown that as the beta cyclodextrin concentration increased from 1 mmol to 1.5 mmol the rate of dissolution increased. However when the amount of beta cyclodextrin decreased to 0.5 mmol the rate of dissolution was higher than 1 mmol but lower than 1.5 mmol. The results similar to what is discussed here has been found in journals. As the BCD amount increases dissolution increases due to drug stability [1] however the higher the amount of BCD the more bulky the compound which means it is harder for the compounds to diffuse through the polymer membrane.

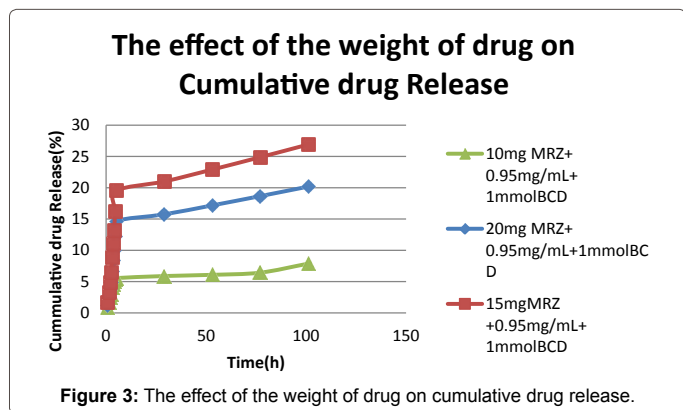
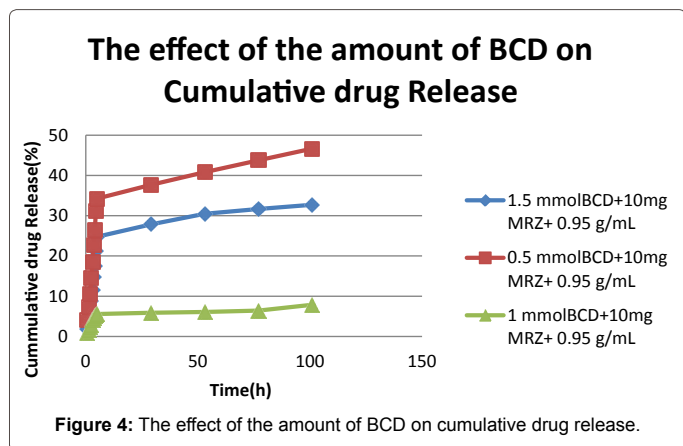


Figure 4 shows as the drug concentration increases from ten milligrams to twenty milligrams the rate of dissolution increases. However the nanoparticles with 15 mg of drug have a higher dissolution rate than those with twenty milligrams of drug. Information similar to this could not be found in journals however one can assume that as the amount of drug increases the BCD cannot incorporate the entire drug which can lead to a lower dissolution rate in comparison to other releases based on concentration.

## Conclusion

In conclusion the entrapment efficiency and drug loading percentage using the double emulsion technique was around 98 percent regardless of the drug concentration, polymer concentration or beta cyclodextrin concentration.



The cumulative release vs time graph showed different dissolution rates depending on what concentration of polymer, concentration of beta cyclodextrin and concentration of drug. As the drug weight increased from 10 mg the dissolution rate increased. However the nanocarrier with 20 mg of drug had a slower dissolution rate then the nanocarrier with fifteen mg of drug. The cumulative release vs. time graph also differed regarding the beta cyclodextrin concentration as the beta cyclodextrin concentration increased from 1mmol to 1.5 mmol there was an increase in drug dissolution. However the beta cyclodextrin concentration of 0.5mmol had a higher dissolution rate than the one mmol nanocarrier. Also when one compares the polymer concentration one can see as the polymer concentration increased the rate of dissolution increased in comparison to 0.95 mmol/mL, however the 2.8 mmol/mL concentrations had a slower dissolution rate then the 1.94 mg/mL concentration.

## Recommendations

Author would recommend that one would use a MRTZ loaded nanocarrier, for the treatment of depression. This will lead to greater bioavailability from BCD as well as the nanocarrier allows for the drug not to be removed from the bodies system. The nanocarrier will also allow for a controlled release of the drug as one can see from Figures 2-4. Due to its controlled release this will reduce the side effects normally experienced by this drug because a controlled concentration of it will be released. If one wants to reduce the amount of drug affecting healthy cells one can add ligands to this nanocarrier which will allow it to specifically target certain cells.

There are several options to creating a controlled release drug; one can vary the polymer concentration and solubizer concentration to get a better controlled release. If one wants a slow release it is best to use the nanocarrier with the concentration of 0.95195 mmol/mL with a BCD weight of 1 mmol because even with a higher concentration of drug it allows for a slow release of the drug over time in comparison the other polymer concentrations.

## Future Work

In the future in order to improve this product one should crosslink specific ligands onto the nanocarriers in order to allow for targeted delivery of the drug. This will improve therapeutic efficacy as well as reduce side effects since the drug will target only specific cells. Also one should find a way to control the size of the nanoparticles.

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