Hydrophobized Microgels for the Delivery of Antipsychotic Drugs to the Brain

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Introduction

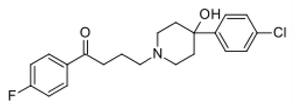
Central nervous system (CNS) diseases affect both the brain and the spinal cord, leading to severe neurological disorders such as schizophrenia, Alzheimer's and Parkinson's disease. Effective treatment of these disorders is a significant challenge given the presence of the blood-brain barrier (BBB), which acts as a protective membrane that is impenetrable to many typical anti-psychotic drugs (APDs) while limiting the potential for IP dosing of other drugs.

Microgels, solvent-swollen networks of covalently cross-linked polymer, can serve as a potential vehicle for the delivery of APDs to the brain. Using free radical precipitation polymerization (FRP), monodisperse populations of microgels with sizes <150 nm ideal for traversing the BBB can be prepared in a single step if a thermoresponsive polymer is used as the primary microgel component. Poly(oligo ethylene glycol) methacrylate (POEGMA) is particularly useful in this context given its biocompatible, nonbiofouling and protein repellent properties[1]. Various comonomers can be incorporated into the formulations to impart targeted properties, such as introducing reactive functional groups for ligand grafting, electrostatic particle stabilization, other "smart" environmental responses, or domains specific to binding target drugs. The selection of the crosslinker determines the degradation mechanism of the microgel[2], while the amount of crosslinker added can tune the degradation rate, rate of drug release, and microgel deformability, which we previously demonstrated can be beneficial for "squeezing" larger microgel particles through the BBB. Thus, by tailoring the microgel formulation for a selected drug and target tissue, the required dosage can be decreased, the therapeutic efficacy can be improved by increasing drug bioavailability at the desired location, and the rate of metabolic clearance can be reduced.[3,4]

There are many potential routes of administration available to introduce therapeutics into the body. Intranasal (IN) administration is among the preferred routes of access when delivering CNS therapeutics when compared to intraperitoneal injection or oral administration, since it provides a non-invasive method of bypassing the BBB to directly deliver drugs to the CNS.[5,6] It is therefore the fastest route of delivery to the brain and results in the highest neural bioavailability.[7,8]

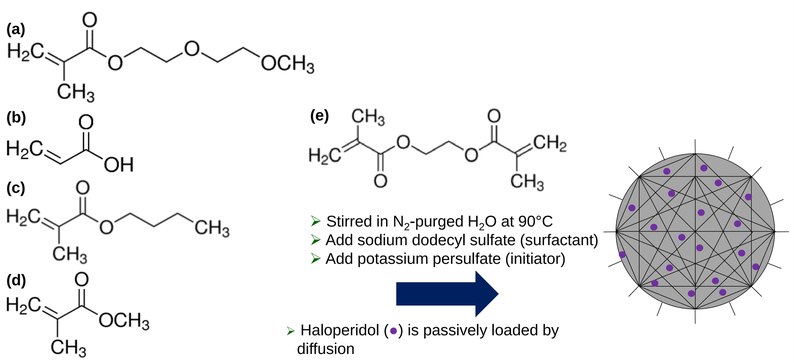
4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one, also known as haloperidol *(Scheme 1)*, is a typical APD used for the treatment of schizophrenia. However, particularly in the context of IN delivery, it suffers from two key limitations: (1) poor aqueous solubility, requiring solvents or acidic buffers to deliver that irritate the nasal mucosa and (2) long-term use associated with tardive dyskinesia, a repetitive, involuntary movement disorder that is incurable. The use of a drug carrier can lessen the risk of this associated negative side effect by decreasing the required dosage of haloperidol required to have a therapeutic effect. Microgels would thus be an ideal delivery vehicle for these drugs, but are typically highly hydrophilic and thus result in poor drug loadings of hydrophobic therapeutics.

In this work, we demonstrate a new method to "hydrophobize" microgels via simple copolymerization of methyl methacrylate (MMA) or butyl methacrylate (BMA) in the conventional microgel recipe. Significantly higher drug loadings result, with the vehicles demonstrated to induce targeted CNS effects without inducing toxicity via both IP and IN administration routes.



Scheme 1. *Chemical structure of haloperidol.*

Experimental



- Stirred in N_2-purged H_2O at 90°C
- Add sodium dodecyl sulfate (surfactant)
- Add potassium persulfate (initiator)

- Haloperidol (●) is passively loaded by diffusion

Scheme 1. *Chemical structures of reactants:*
(a) diethylene glycol methacrylate*, a monomer leading to a thermoresponsive polymer*
(b) acrylic acid, *which enhances colloid stability and provides reactive sites for grafting*
(c) butyl methacrylate *or* ***(d) methyl methacrylate,*** *hydrophobic monomers*
(e) ethylene glycol dimethacrylate, *an example of one of many degradable crosslinkers that can be used*

Microgel characterization:
- Dynamic light scattering (size/size distribution)
- Electrophoretic mobility (surface charge density)
- Conductometric titration (functional acid content)

Evaluation of catalepsy induction:
- Front paws of were placed in an extended position on a 10 cm high horizontal bar
- Scored 0-3 based on time spent on the bar: 0 = < 20 s, 1 = 20–40 s, 2 = 40–60 s, 3 = > 60 s.

Evaluation of motor suppression induction:
- Movement was recorded in a locomotion chamber using a laser-assisted apparatus

Microgel Characterization

Table 1. *Physical and chemical characteristics of microgel formulations containing various mole percentages of butyl methacrylate.*

Sample (mol %)	Diameter (nm)	Polydispersity	Mobility (μ/s)/(V/cm)
10% BMA	67 ± 1	0.04	-0.7 ± 0.4
15% BMA	65 ± 1	0.06	-0.2 ± 0.4
20% BMA	75 ± 4	0.06	-1.5 ± 0.1
25% BMA	115 ± 8	0.30	-1.3 ± 0.1

Table 2. *Physical and chemical characteristics of microgel formulations containing various mole percentages of methyl methacrylate.*

Sample (mol %)	Diameter (nm)	Polydispersity	Mobility (μ/s)/(V/cm)
10% MMA	79 ± 1	0.05	-0.9 ± 0.1
15% MMA	77 ± 3	0.04	-0.7 ± 0.1
20% MMA	89 ± 5	0.05	-0.7 ± 0.2
25% MMA	68 ± 3	0.07	0 ± 0.9

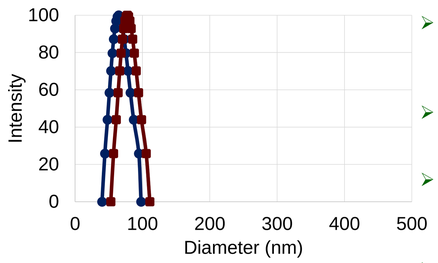


Figure 1. *Comparison of size distribution of microgels containing 15 mol% of either BMA (●) or MMA (■).*

- Hydrophobized microgels synthesized via FRP are small (<100 nm), monodisperse (PD <0.1) and colloidally stable.
- The small anionic charge is due to the incorporation of acrylic acid on or near the surface (useful for ligand targeting).
- Due to the greater hydrophobicity of BMA, these formulations are consistently smaller than MMA microgels.
- Increasing the quantity of hydrophobic monomer beyond a maximum produces larger and more polydisperse microgels.

Drug Loading

Table 3. *Uptake of haloperidol as a function of hydrophobic monomer content*

Hydrophobic Monomer Content (mol %)	Drug Concentration (μg drug/mg microgel)	
	BMA	MMA
15	21	29
20	8	15
25	5	8

Table 4. *Entrapment efficiency (%) and concentration of loaded drug (mass drug/volume) for two hydrophobic drugs, curcumin (2 mg/mL) and haloperidol (4 mg/mL).*

	Entrapment Efficiency (%)		Drug Concentration (mg/mL microgel suspension)	
	Curcumin	Haloperidol	Curcumin	Haloperidol
15% BMA	9.5	8.6	0.10	0.83
15% MMA	12.0	11.0	0.18	1.10

- Adding hydrophobic comonomers significantly increases drug loading versus unfunctionalized microgels, but microgel collapse induced at higher hydrophobic comonomer contents or by more hydrophobic comonomers (i.e. BMA versus MMA) limits the drug loading benefits.

Evaluation of Locomotion Impairment

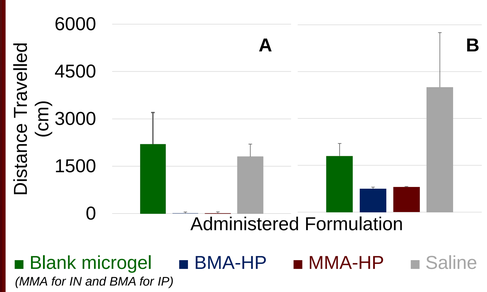


Figure 2. ***Effect of administered therapeutic on locomotion suppression in rats.*** *Panel A shows results after intranasal administration and panel B shows results after intraperitoneal injection.*

- Hydrophobized microgel delivery of haloperidol induces effective suppression of locomotion in rats, particularly when delivered via the IN route.

Evaluation of Catalepsy

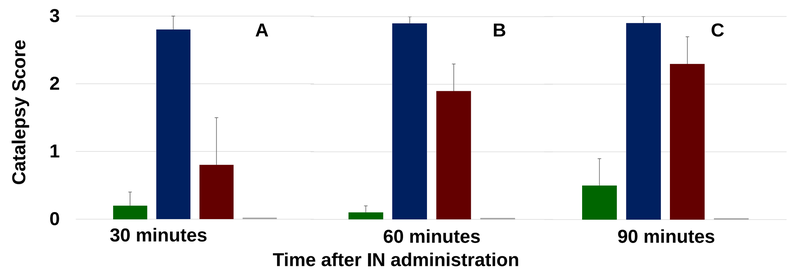


Figure 3. *Behavioral effects induced following IN administration of drug-loaded formulation.*

- Both MMA- and BMA-functionalized microgels can induce catalepsy in rats, although the smaller size and higher hydrophobicity of BMA-functionalized microgels results in more rapid onset of catalepsy via IN route.

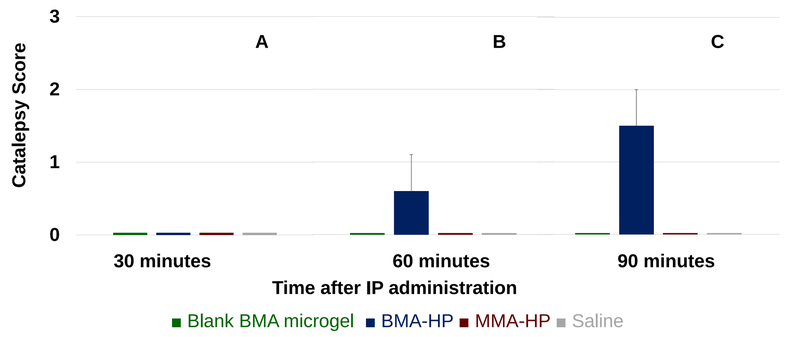


Figure 4. *Behavioral effects induced following IP injection of drug loaded formulation*

- IN delivery is more effective than IP delivery in facilitating microgel-mediated drug transport to the brain → IN route bypasses first pass metabolism and other circulation-based clearance mechanisms

Conclusions

- Hydrophobized POEGMA-based microgels containing either BMA or MMA can be synthesized via FRP to produce small, monodisperse populations of particles with ideal properties for crossing the BBB.
- Lower quantities of MMA permit greater drug loading than more microgels with higher MMA contents or the ore hydrophobic BMA monomer, as uptake depends on both microgel hydrophobicity and microgel collapse.
- Haloperidol-loaded POEGMA microgels can be effectively delivered to the brain via IN administration and are able to cause significant immediate and lasting pharmacological effects.
- Since no safe and non-toxic ways are available to deliver haloperidol and other hydrophobic drugs via the IN route, haloperidol-loaded microgels have potential clinical utility due to their non-toxicity and low cost.

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