

Unit 1: Green Chemistry: Microwave, Ultrasound and Continuous Flow Synthesis

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Advanced Organic Chemistry II, subject code MPC202T, is a core Semester 2 subject of M.Pharm Pharmaceutical Chemistry. It carries 4 credits and 60 hours of theory, taught at 4 hours per week, for 100 marks. Where Advanced Organic Chemistry I (MPC102T) taught how reactions work, this subject teaches how modern synthesis is actually practised. Unit 1 covers green chemistry and the three enabling technologies that have changed how reactions are heated, mixed and scaled: microwave irradiation, ultrasound and continuous flow reactors. Unit 2 is the chemistry of peptides, from coupling reagents and the racemisation problem through Merrifield solid phase synthesis in its Boc and Fmoc forms to solution phase strategies and side reactions. Unit 3 treats reactions driven by light and reactions governed by orbital symmetry: photo-oxidation, photo-addition and photo-fragmentation, then the pericyclic family of cycloadditions, electrocyclic reactions and sigmatropic rearrangements. Unit 4 is catalysis in all its forms: heterogeneous, homogeneous, transition metal, organo, bio and phase transfer catalysis, each with the examples drug synthesis actually uses. Unit 5 returns to stereochemistry at full depth: optical activity, the CIP rules, meso and pseudoasymmetric centres, D and L notation, E and Z notation, resolution of racemates, and the three great strategies of asymmetric synthesis, chiral pool, chiral auxiliaries and chiral catalysts. A student who completes this subject should be able to choose a greener way to run a reaction, plan a peptide synthesis and predict its side products, assign the stereochemical course of a pericyclic reaction, pick a catalyst class for a transformation, and design a route to a single enantiomer.

1.1 Why synthesis needed a greener logic

Classical organic synthesis was judged by one number: yield. The waste a process generated, the solvents it consumed and the hazard it carried were someone else's problem. The pharmaceutical industry made this impossible to ignore, because drug molecules are complex, their syntheses are long, and the waste per kilogram of product is the highest in the chemical industry. Roger Sheldon quantified this with the **E factor**, the kilograms of waste produced per kilogram of product. His classic comparison puts oil refining near 0.1, bulk chemicals at about 1 to 5, fine chemicals at 5 to 50 and pharmaceuticals at 25 to 100 or more. Solvents are the largest single part of that waste, typically 80 to 90 percent of the mass of a pharmaceutical process. Green chemistry, formalised by Paul Anastas and John Warner in 1998, is the design discipline that attacks the problem at source: a process that never makes waste does not have to treat it.

1.2 The twelve principles of green chemistry

The twelve principles are the syllabus in miniature; almost every topic in this unit is one of them in action.

- 1 **Prevention:** it is better to prevent waste than to treat or clean it up after it is formed.
- 2 **Atom economy:** synthetic methods should maximise the incorporation of all materials used into the final product.
- 3 **Less hazardous chemical syntheses:** methods should use and generate substances with little or no toxicity.
- 4 **Designing safer chemicals:** products should achieve their function while minimising toxicity.

- 5 **Safer solvents and auxiliaries:** auxiliary substances (solvents, separation agents) should be unnecessary where possible and innocuous where used.
- 6 **Design for energy efficiency:** energy requirements should be minimised; reactions should run at ambient temperature and pressure where possible.
- 7 **Use of renewable feedstocks:** a raw material should be renewable rather than depleting where technically and economically practicable.
- 8 **Reduce derivatives:** unnecessary derivatisation (blocking groups, protection and deprotection, temporary modification) should be minimised or avoided, because it consumes reagents and creates waste.
- 9 **Catalysis:** catalytic reagents, as selective as possible, are superior to stoichiometric reagents.
- 10 **Design for degradation:** chemical products should break down at the end of their function into innocuous substances.
- 11 **Real time analysis for pollution prevention:** analytical methods should allow in-process monitoring and control before hazardous substances form.
- 12 **Inherently safer chemistry for accident prevention:** substances and processes should be chosen to minimise the potential for explosions, fires and releases.

Unit 4 of this subject is principle 9 expanded; the microwave, ultrasound and flow methods below are principles 5 and 6 in hardware form; and the protecting group discipline of Unit 2 exists partly because principle 8 says every protection step that can be avoided should be.

1.3 Measuring greenness: atom economy and the E factor

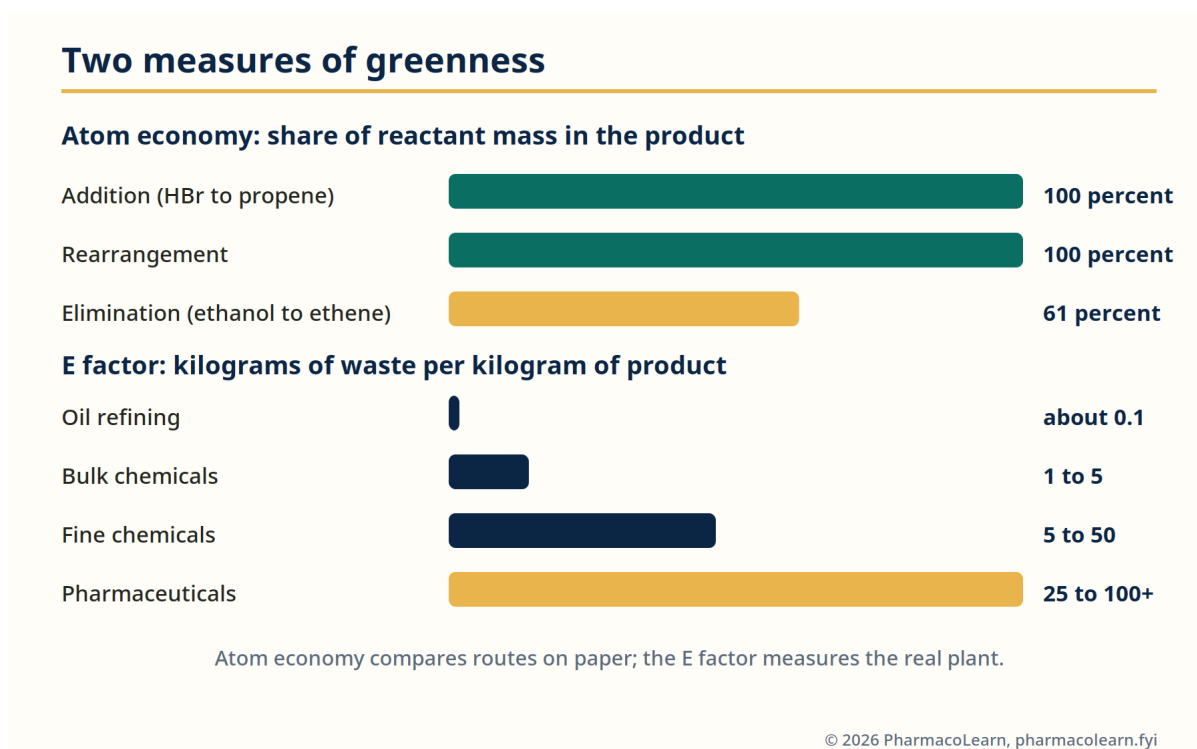


Figure: Atom economy rewards additions and rearrangements; the E factor shows why pharmaceutical processes, with E factors of 25 to 100 or more, are the prime target for greener design.

Atom economy (Trost) is calculated before a reaction is ever run: atom economy = (molecular weight of the desired product divided by the sum of the molecular weights of all reactants) multiplied by 100. Addition and rearrangement reactions score 100 percent in principle, because every reactant atom appears in the

product. Substitution and elimination reactions necessarily lose atoms as leaving groups or small molecules. A quick example: dehydration of ethanol to ethene gives 28 divided by 46, an atom economy of about 61 percent, the rest leaving as water; addition of HBr to propene gives 100 percent, because the only product is the bromoalkane. Atom economy ignores yield, excess reagents and solvents, which is where the **E factor** and its relative, process mass intensity (total mass in per mass of product), take over. A wise process chemist quotes both: atom economy to compare routes on paper, E factor to compare plants in practice.

1.4 Microwave assisted reactions: how the heating works

A domestic or laboratory microwave field oscillates at 2.45 GHz, and it heats by **dielectric heating** through two mechanisms. In **dipolar polarisation**, molecules with a permanent dipole (water, alcohols, DMF) try to follow the oscillating field; their rotation lags the field, and the friction of that lag is dissipated as heat throughout the whole volume at once. In **ionic conduction**, dissolved ions are dragged back and forth through the solution and collide with solvent molecules, again generating heat. The efficiency of a solvent is summarised by its loss tangent, $\tan \delta$: ethanol (about 0.94), DMSO (about 0.83) and methanol are strong absorbers; water (about 0.12) is moderate; acetonitrile is weak; toluene (about 0.04) and hexane are almost transparent. Unlike an oil bath, which heats the vessel wall and relies on conduction and convection, microwave energy is deposited directly in the reaction mixture, so the contents can be hotter than the walls: the temperature gradient is inverted.

1.5 Why microwave reactions are fast: rates, superheating and solvent effects

Three effects combine to give the rate increases, often hours compressed into minutes, that the syllabus asks about.

- **Rapid, uniform core heating:** the mixture reaches the set temperature in seconds, so none of the reaction time is wasted climbing a slow thermal ramp.
- **Superheating:** in a sealed vessel the solvent can be held far above its normal boiling point, since pressure rises instead of boiling occurring; a reaction in ethanol at 180 degrees Celsius in a sealed microwave vessel is routine, and by the Arrhenius equation each 10 degree rise roughly doubles the rate, so the rate gains are large and entirely thermal in origin. Claims of mysterious non-thermal "specific microwave effects" have largely been traced to exactly these thermal and wall effects when temperature is measured properly with internal probes.
- **Solvent effects:** the solvent is the heating element. Polar solvents and ionic reagents couple strongly and heat fast; non-polar solvents heat poorly unless a susceptor is added (a strongly absorbing material such as silicon carbide or graphite, or a passive heating element in the vessel). Ionic liquids, being entirely ionic, absorb extremely well. Reactions can also be run neat or on solid supports (alumina, silica, clays), where adsorbed polar reactants absorb the field selectively, combining microwave heating with the solvent-free ideal of principle 5.

Merits: dramatic time savings, frequently higher yields and cleaner product profiles (less time at temperature means fewer decomposition products), energy efficiency, reproducibility in dedicated single-mode reactors, and rapid optimisation because dozens of conditions can be screened in an afternoon. **Demerits:** the field penetrates only a few centimetres into an absorbing mixture, so batch scale-up is limited and large-scale work moves to flow or multimode systems; sealed vessels carry pressure hazards; equipment is costly; and temperature measurement is less direct than sticking a thermometer in a flask. Microwave technology earns its place in process optimisation precisely as a discovery and screening engine: find the fast, clean, high-temperature conditions in the microwave, then transfer them to a flow reactor (section 1.9) for production.

1.6 Microwave synthesis in practice

Microwave conditions have been applied across the standard reaction repertoire: condensations, cycloadditions, metal catalysed cross couplings that complete in minutes, and alkylations under phase transfer conditions. The showcase applications are in **heterocycle synthesis**, where the cyclisation step is often slow and high temperature: the Biginelli dihydropyrimidinone synthesis, Hantzsch pyridine and dihydropyridine syntheses, imidazole, thiazole and pyrazole ring closures, and quinoline syntheses all run in minutes under microwave irradiation, frequently in water or ethanol rather than in high-boiling toxic solvents. This matters to the pharmaceutical chemist because most drug scaffolds are heterocyclic (Unit 4 of MPC102T): the microwave has become the default tool for building analogue libraries of heterocycles during drug discovery.

1.7 Ultrasound assisted reactions: acoustic cavitation

Ultrasound in synthesis means sound at frequencies above human hearing, usually 20 to 100 kHz from a cleaning bath or an immersion probe. Its chemistry comes not from the sound wave itself but from **acoustic cavitation**: in the low-pressure half-cycle of the wave, microscopic bubbles form and grow in the liquid; in the compression half-cycle they collapse violently. The collapse concentrates the energy of the wave into tiny hot spots estimated at roughly 5000 K and pressures of the order of 1000 atmospheres, lasting microseconds, with extreme heating and cooling rates. Near a solid surface the collapse is asymmetric and launches a microjet of liquid at the surface, which cleans, pits and activates it. Two consequences follow: in homogeneous solution, cavitation can generate radicals and switch reaction pathways (sonochemical switching); in heterogeneous systems, the dominant effects are mechanical, surface activation, particle size reduction and intense local mixing, sometimes called false sonochemistry because the chemistry itself is ordinary.

1.8 Types of sonochemical reactions

The syllabus divides sonochemical reactions by phase behaviour:

- **Homogeneous liquid phase reactions:** cavitation inside a single liquid phase produces radicals and excited species; the classic examples are the decomposition of volatile organometallics and aqueous sonolysis, in which water is split into hydrogen atoms and hydroxyl radicals that can drive oxidations. True sonochemistry, radical in character.
- **Heterogeneous liquid-liquid reactions:** two immiscible liquids, where ultrasound emulsifies the mixture into a fine dispersion, multiplying the interfacial area so that reactions normally needing a phase transfer catalyst can proceed faster, or with less catalyst; examples include ester hydrolyses and the generation of dichlorocarbene from chloroform and aqueous alkali.
- **Heterogeneous liquid-solid reactions:** a solid reactant or catalyst in a liquid, where microjets strip passivating layers and expose fresh surface. This is the most synthetically valuable class: formation of organometallic reagents that are sluggish conventionally, such as the Barbier reaction (carbonyl plus alkyl halide plus metal in one pot) and the Reformatsky reaction (zinc and an alpha-bromo ester), both dramatically improved by sonication; also lithium and magnesium activation, and hydrogenations over catalysts whose surfaces stay clean.

1.9 Continuous flow reactors: working principle

In a flow reactor the reagents are pumped continuously through a channel, coil or packed bed of small internal volume, reacted for a defined **residence time** (reactor volume divided by total flow rate: a 10 mL coil at 1 mL per minute gives every molecule a 10 minute reaction), and the product stream exits to be

collected or fed into the next step. Small channels have a very high surface area to volume ratio, so heat transfer and mixing are excellent; a back pressure regulator lets solvents be superheated safely, like a microwave vessel but continuously; and at any instant only a few millilitres of reaction mixture exist, so hazardous intermediates (azides, diazo compounds, nitration mixtures, ozonolysis) are generated and consumed in small, controlled amounts, the concept Yoshida calls flash chemistry when residence times are seconds and reactive organolithium species are used before they can decompose.

1.10 Flow reactors: advantages and synthetic applications

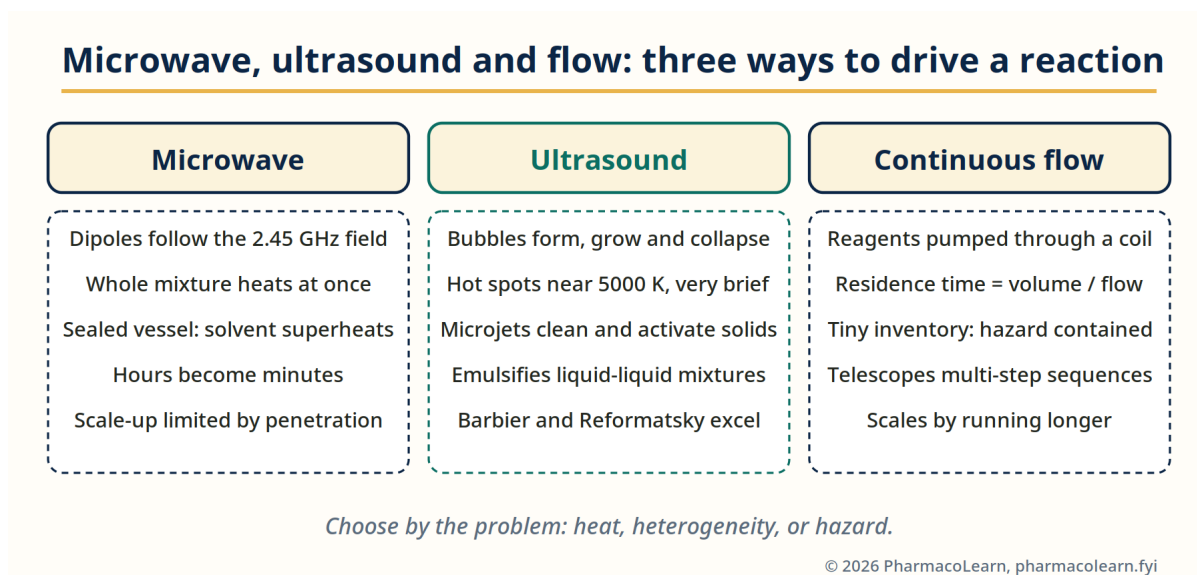


Figure: Three physical ways to drive reactions: microwave heats dielectrically, ultrasound works through cavitation, and flow reactors work through controlled residence time.

Advantages: safety at small inventory; precise control of temperature, mixing and reaction time, hence reproducibility; easy automation and in-line analysis (principle 11); scale-up by running longer or numbering up parallel channels rather than redesigning a vessel; and the ability to telescope several steps into one continuous sequence with no isolation of intermediates. **Applications:** continuous nitration and hydrogenation at production scale, photochemical steps in transparent flow coils (section 3.2), exothermic organometallic chemistry, and complete multi-step API syntheses in a single flowing stream: literature demonstrations include continuous routes to ibuprofen and to artemisinin. Flow is where microwave discovery conditions most often end up when a process group adopts them, so the two technologies of this unit are partners, not rivals.

Feature	Microwave batch	Ultrasound	Continuous flow
Energy input	Dielectric heating of the whole mixture	Acoustic cavitation, local hot spots and jets	Conductive heating of a small flowing volume
Best at	Fast screening, heterocycle synthesis, superheated solvents	Heterogeneous mixtures, metal activation, emulsions	Scale-up, hazardous steps, multi-step sequences
Scale limit	Penetration depth of the field, vessel size	Bath and probe are bench scale	Run longer or number up, production proven
Main hazard	Pressure in sealed vessels	Probe erosion, noise, radical pathways	Blockages, pressure control
Green principle served	Energy efficiency (6)	Safer solvents, catalysis (5, 9)	Inherent safety, real time analysis (11, 12)

Choosing an enabling technology for a difficult step

Is the step slow mainly because it needs high temperature?

-> microwave for screening; transfer the conditions to flow for scale

Is the mixture heterogeneous, with a passivated metal or two liquid phases?

-> ultrasound, for surface activation and emulsification

Is the step hazardous, very exothermic, or one of several steps in a row?

-> continuous flow, small inventory and telescoping

Is the problem simply a poor solvent?

-> change the solvent first; technology cannot fix a bad solvent choice

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