Trends in oral solid dosage forms: Review of 2017-2019 EMA approvals

Background

Publicly available regulatory agency documents, such as EPARs (European public assessment reports), are a valuable source of CMC data on drug products; the extent of information disclosed within such documents has increased notably in recent years. A review of EPARs for 2017, 2018 and 2019 is summarised in this post and provides an interesting insight into the formulation development strategies being adopted for orally administered NCEs.

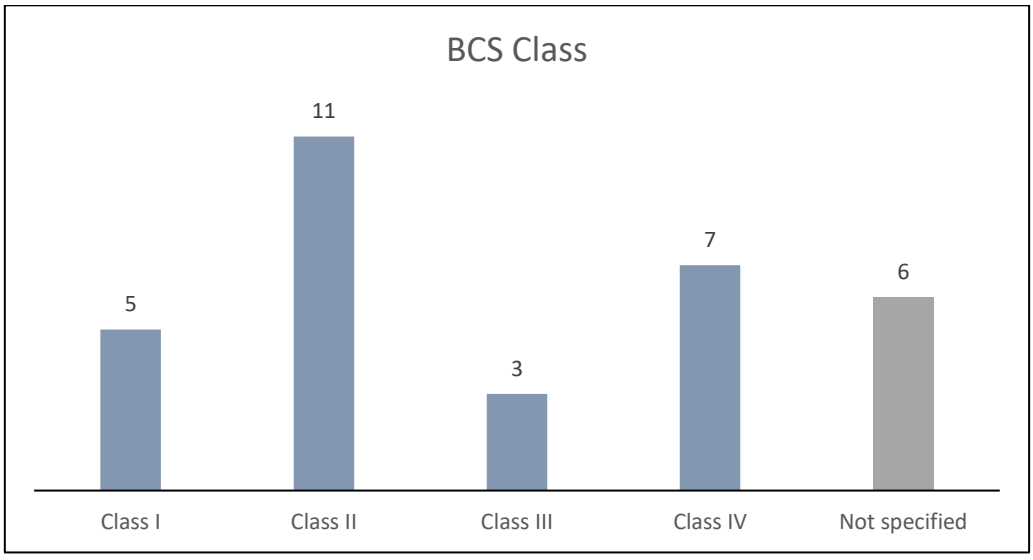
Thirty-two of the new medicines approved by the EMA in the period 2017-19 were orally administered solid dosage forms containing a single NCE; these medicines are the subject of this review. Any combination products containing NCEs are excluded.

Drug Substance

Seventeen of the thirty-two NCEs are in the form of salts; the most common salt forms are hydrochloride and tosylate (three NCEs for each). Two NCEs are described as co-crystals (with L-pyroglutamic acid and fumaric acid respectively).

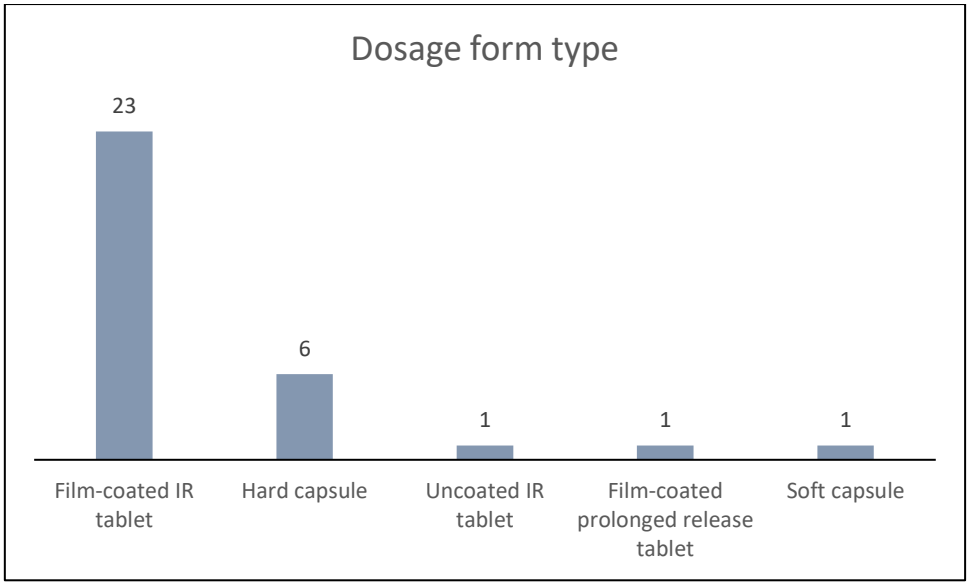
Two of the NCEs are pro-drugs and provide enhanced bioavailability compared to the active moieties.

The majority of the NCEs are categorised as BCS Class II (low solubility, high permeability).



Tablets vs. Capsules

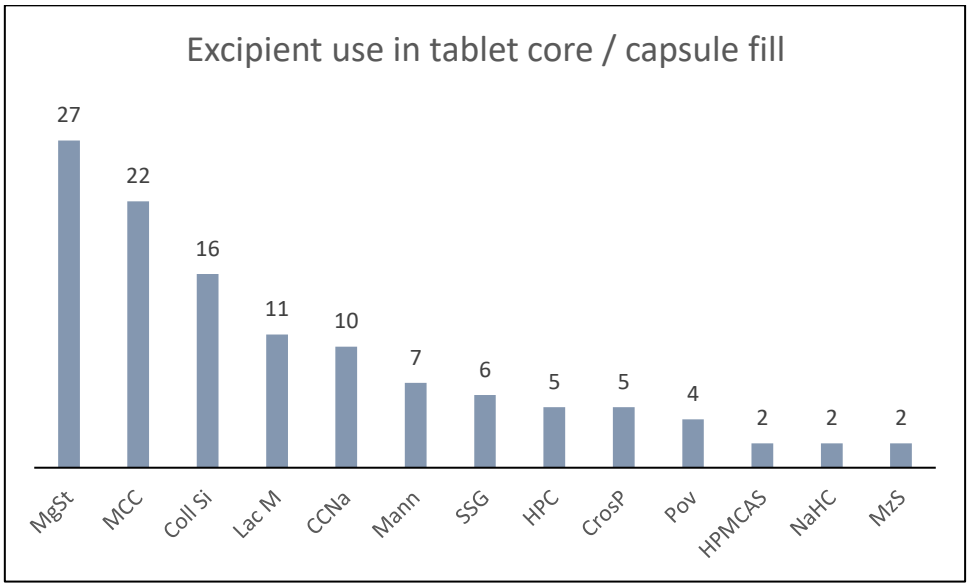
Unsurprisingly, film-coated immediate-release (IR) tablets are the predominant dosage form. One tablet is a prolonged release formulation (matrix containing hypromellose) in order to enable once-daily administration of a drug with a short half-life.



Excipients

One hard capsule formulation comprises drug substance alone with no excipients.

Excipients appearing in two or more of the formulations are presented in the chart below; only the excipients present in the tablet core or capsule fill are included i.e. any coating ingredients are excluded.



MgSt = magnesium stearate; MCC = microcrystalline cellulose; Coll Si = colloidal silica; Lac M = lactose monohydrate; CCNa = croscarmellose sodium; Mann = mannitol; SSG = sodium starch glycolate; HPC = hydroxypropyl cellulose (including “L” grades); CrosP = crospovidone; Pov = povidone; HPMCAS = hypromellose acetate succinate; NaHC = sodium hydrogen carbonate; MzS = maize starch

Excipients appearing in fewer than two formulations are sodium dihydrogen phosphate, citric acid, calcium hydrogen phosphate, glyceryl behenate, talc, hypromellose, anhydrous lactose, tartaric acid, copovidone, poloxamer 188, succinic acid, sodium stearyl fumarate,

macrogolglycerol hydroxystearate, macrogol, ethanol, maize oil mono-di-triglycerides, and α-tocopherol.

Amorphous solid dispersion (ASD)

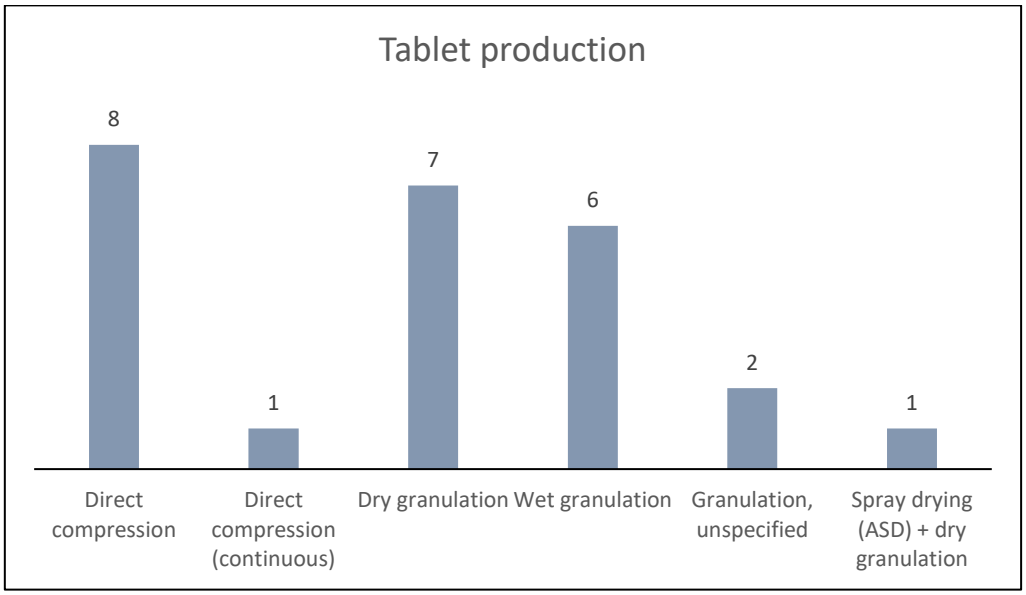
Three of the formulations (two tablets and one hard capsule) contain drug in the form of an ASD; the drugs in question are all BCS Class II. Two of the formulations use HPMCAS as the stabilising polymer and one uses a copovidone/poloxamer 188 mixture; the latter ASD is believed to be prepared by hot-melt extrusion.

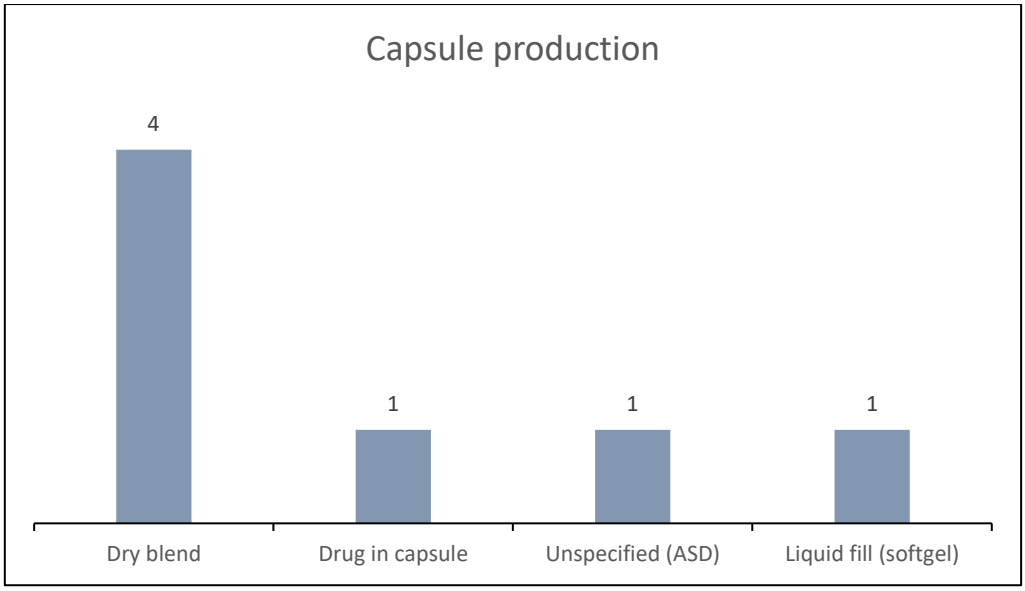
Manufacturing process

For tablets, there is a fairly even division between direct compression, dry granulation and wet granulation processes. The tablet cores for one product are made using a continuous process.

The capsules are predominantly prepared as a dry blend of drug and excipients.

There is no mention of drug substance micronisation for any of the products.





Comments

The NCE formulations are primarily conventional. The use of solubility-enhancing delivery technologies was confined to three products in which the drug was present as an amorphous solid dispersion and one soft capsule in which the drug was formulated as a self-emulsifying system.

Speed to market is critical when selecting a formulation for an NCE and so low risk or proven technologies will always be preferred. A proprietary formulation technology will clearly be much more attractive to a pharma company if a process for rapid screening and evaluation is available so it can quickly be established if it offers an effective route for solubility or bioavailability enhancement.