New Prospects for Therapeutic Organic Nanocrystals - Supporting file

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Table 1. Approved NCs (updated from Lu *et al.*[71] and Couillaud *et al.*[1] reviews

	Trade name	API	Company	Therapeutic indication	Manufacturing approach	Approval date	Approved Agency	Admin. route
ORAL	Avinza®	Morphine sulfate	King Pharm	Antichronic pain	Top–down, media milling	2002	FDA	Oral
	Cesamet®	Nabilone	Lilly	Antiemetic	Bottom–up, coprecipitation	2005	FDA	Oral
	Emend®	Aprepitant	Merck	Anti-emetic	Top–down, media milling	2003	FDA	Oral
	Focalin XR®	Dexmethyl-phenidate HCl	Novartis	Antipsychotic	Top–down, media milling	2001	FDA	Oral
	Gris-Peg®	Griseofulvin	Novartis	Antifungal	Bottom–up, coprecipitation	1982	US FDA	Oral
	Herbesser®	Diltiazem	Mitsubishi Tanabe Pharma	Antiangina	Top–down, media milling	2002	Japanese Ministry of Health	Oral
	Megace ES®	Megestrol	Par Pharmaceutical Companies	Anti-anorexic	Top–down, media milling	2005	FDA	Oral
	Naprelan®	Naproxen sodium	Wyeth	Anti-inflammation	Top–down, media milling	2006	FDA	Oral
	Rapamune®	Rapamycin	Wyeth	Immuno-supressant	Top–down, media milling	2000	FDA	Oral
	Ritalin LA®	Methyl-phenidate HCl	Novartis	Antipsychotic	Top–down, media milling	2002	FDA	Oral
	Skelaxin[68]	Metaxolone	King Pharm	Skeletal-muscular pain	Top–down, media milling	2002	FDA	Oral

	Theodur®	Theophylline	Mitsubishi Tanabe Pharma	Bronchial dilation	Top–down, media milling	2008	FDA	Oral
	Tricor®	Fenofibrate	Abbott	Hypercholesterolemia	Top–down, media milling	2004	FDA	Oral
	Triglide®	Fenofibrate	Sciele Pharma Inc.	Hypercholesterolemia	Top–down, high-pressure homogenization	2005	FDA	Oral
	Verelan PM®	Verapamil	Schwarz Pharma	Anti-arrhythmia	Top–down, media milling	1998	FDA	Oral
	Yonsa®[69]	Abiraterone acetate	Sun Pharma Global FZE	Metastatic castration-resistant prostate cancer	Top–down, media milling	2018	FDA	Oral
	Zanaflex™	Tizanidine HCl	Acorda	Muscle relaxant	Top–down, media milling	2002	FDA	Oral
PARENTERAL								
	Aristada Initio®[44], [70]	Aripiprazole Lauroxil	Alkermes	Schizophrenia	Top–down, media milling	2015	FDA	i.m.
	Cabenuva®	Cabotegravir and rilpivirine (co-packaged)	Viiv healthcare	HIV-1		2021	FDA	i.m.
	Invega Sustenna®	Paliperidone palmitate	Janssen	Antipsychotic	Top–down, high-pressure homogenization	2009	FDA	i.v./i.m.
	Zyprexa Relprevv®[44]	Olanzapine pamoate	Eli Lilly	Schizophrenia		2010	FDA	i.m.
OTHERS								
	Azopt®[9]	Brinzolamide	Alcon	Glaucoma	Top–down, media milling	1998	FDA	ocular

Table 2. Examples of monocrystals prepared by bottom-up approaches reported in the literature for various medical applications: administration route, preparation mode, and stabilizer involved

Therapeutics area	Therapeutic indication	API	Admin. route	Preparation	Stabilizer	Particle Size (nm)	Reference
Cancer	H22 sarcoma, preclin.	Hydrocamptothecin	i.v.	ASP/US	FCS	168 ± 3	[72]
Cancer	Lung metastases MDA-MB-231	Campothecin	i.v.	ASP/US	pH 4	250 ± 16	[73]
Cancer	Antitumor/Antioxidant	Curcumin	i.v.	ASP/HPH		199	[74]
Cancer	Antineoplastic	Bexarotene	Oral	ASP/HPH	P188/Lecithin	200	[75]
Cancer	Immune regulator	Monosodium urate		ASP	DMEM 10%	26–137	[76]
Cancer	B16F10; SKOV-3 cells;	Docetaxel	In vitro	ASP	F127/Albumin	284 ± 96	[48]
Cancer	MDA-MB-231, MCF-7, HCC1943, HCC1937 cells; 4T1 orthotopic breast cancer model	Carfilzomib	i.v.	Film hydration/US	F127/Albumin	270–328	[77]
Cancer	G361 melanoma- cells; In vivo B16 melanoma	Paclitaxel	i.v.	ASP/microfluidic	Carboxymethyl Chitosan	230 ± 90	[45]
Cancer	HCT116, HT29 Colorectal cancer cells	Salinomycin	Oral	ASP/US	HPMC	210 ± 10	[78]
Cancer	Lung and colon cancer, 3LL and CT26 cell lines	Etoposide	i.v.	ASP	P407 and P407/Albumin	117 ± 28	[15]
Cancer	Non-small cell lung cancer, pK	Nintedanib	Oral	ASP/US	CMC-Na	325 ± 1	[79]
Cancer	Cytotoxicity on 3LL and human endothelial (EA.hy926) cell lines	Fisetin	In vitro	ASP	P407	148 ± 1	[16]

Cancer	Lewis lung carcinoma (LLC) xenograft model	Etoposide	Oral	ASP + HPH	Lipid encapsulation	220 ±14	[80]
Inflammation	pK and blood concentration	Breviscapine	i.m.	ASP/US	Poly(lactic-co-glycolic acid) loading	micro-particles	[81]
Inflammation	Antinociceptive activity in acetic acid-induced abdominal constriction assay	Acecoflenac	Oral	ASP/US	PVP/HPMC /SLS	112 ± 2	[82]
Inflammation	Anti-inflammatory	Budenoside	Oral, pulmonary	ASP	Mannitol	440	[83]
Inflammation	Anti-inflammatory	Meloxicam	Sublingual	ASP	Polysorbate 80 / Poloxamer 407	180	[84]
other	Antifungal	Itraconazole	Oral	Acid-base neutralization Spray drying	P407 or HPMC	267	[85]
other	Lowering triglycerides	Fenofibrate	Oral	ASP/thermal precipitation	Polysorbate 80 / PEG / PVP-K30 / Tragacanthe	>1000	[52]
other	Erectile dysfunction	Avanafil	Oral	ASP/US	Tween 80/PVA/P188	128-4868	[86]
other	HIV therapy	Efavirenz	Oral	ASP/US	HPMC/PVP	161–5267	[87]
other	Antidiabetic	Glibenclamide	Transdermal	ASP/HPH	Chitosan	429	[88]
other	Prevention of age-related macular degeneration	Lutein	Oral fast dissolving Film	ASP	HPMC/PEG400/Cremophor EL	377	[89]
other	Angiotensin II receptor antagonist	Olmesartan medoxomil	Oral	ASP/HPH	TPGS / F68	140 ± 10	[90]

Table 3: Co-nanocrystals described so far in the literature.

Therapeutic indication(s)	APIs	Admin. route	Preparation	Stabilizer	Particle Size (nm)	Reference
Anticancer, anti-inflammatory	Baicalein / Nicotinamide	Oral	HPH	P188	252 ± 9	[56]
Anti-HIV	Lamivudine / Zidovudine	Oral	cold-US	Span80	352 ± 21	[91], [92]
Anti MDR cancer	Paclitaxel / Disulfiram	i.v.	ASP + US	β-lactoglobulin	160	[60]
Anti MDR cancer	Paclitaxel / Lapatinib	*In vitro*	ASP	Polydopamine/PEG	171 ± 1	[61]
Anti MDR cancer	Etoposide/Prednisolone	*In vitro*	ASP	P407	181 ± 9	[6]

Table 4: Reported targeting Nanocrystals

Target	API	Application	Ligand	Coupling	Year	Reference
Transferrin receptor	Camptothecin	Tumors expressing Tf	Peptide T7	peptide coupled to polydopamine	2017	[62]
HER receptor	Paclitaxel	Breast cancer	Herceptin	noncovalent	2016	[93]
CD44	Paclitaxel	Lung metastases	Hyaluronic acid	Noncovalent interaction	2016	[64]
CD44	Curcumin	Breast cancer	Hyaluronic acid	Noncovalent interaction	2016	[94]
CD44 and Tf receptor	Paclitaxel	Breast cancer	Hyaluronic acid or ApoTf	Grafting	2017	[63]
Integrin	Paclitaxel		RGD	Conjugation to polydopamine	2019	[95]
Mitochondria	Paclitaxel	MDR cells	TPP	Conjugated to Brij 98	2019	[96]
Folate receptor	Paclitaxel	Breast Cancer	Folic acid	Membrane wrap NCs	2021	[97]
Folate receptor	Paclitaxel	Hepatoma	Folic acid	Membrane wrap NCs	2022	[66]
HER-2	Paclitaxel	Breast cancer	Herceptin	SK-BR-3 Membrane wrap	2022	[65]
CD44	Indirubin	Psoriasis	Hyaluronic acid	Milling, HA	2023	[98]

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