Contents lists available at ScienceDirect

Chemical Engineering Research and Design

journal homepage: www.elsevier.com/locate/cherd

A review on novel methodologies for drug nanoparticle preparation: Microfluidic approach

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ARTICLE INFO

Article history:
Received 1 August 2019
Received in revised form 23 November 2019
Accepted 25 November 2019
Available online 30 November 2019

Keywords:
Controlled drug delivery
Microfluidics
Spray drying
High pressure homogenization
Ultrasonication

ABSTRACT

The intrinsic limitations of conventional dosages have facilitated the emergence of novel drug delivery methodologies. Drug nanonization and encapsulation in polymeric biomaterials offers a new platform to enhance therapeutic efficiency and patient compliance. The two most basic approaches for drug size reduction are top-down, bottom-up, or a combination of these methods. This review analyzes three widely investigated techniques (viz. spray drying, high pressure homogenization, and ultrasonication) along with microfluidics for drug nanonization and encapsulation in past few years. Also, the existing challenges of aforesaid methodologies and their solution through microfluidics are highlighted. Microfluidics has brought unique opportunities towards complete control over process parameters, owing to miniaturization of fluidic environment. Overall, the emergence of microfluidic technology has created exciting possibilities in the field of controlled drug delivery and has paved a way for clinical translation of nanomedicines.

Contents

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https://doi.org/10.1016/j.cherd.2019.11.031

1. Introduction

Novel drug delivery methodologies have started to emerge over the conventional dosage forms aiming to enhance therapeutic efficiency and patient compliance. The novel drug delivery approaches seek to reduce the cost involved in new drug development, drug side-effects and to improve the affinity to controlled release (Kumar et al., 2012). The novel drug delivery methods include the controlled release, sustained release, and targeted release dosage. To date, more than 80 applications of nanocrystals have been submitted to the US Food and Drug Administration (USFDA). These therapeutics can be delivered through various routes of administration – 63% of the applications are for the oral route of drug administration (Chen et al., 2017). Drug delivery through pulmonary and nasal tract has also gained significance with ongoing research and development. To ease the drug administration, patient compliance and to provide the flexibility of design of dosage; oral route of delivery is preferred the most in comparison to other methods (Mali et al., 2015). About 40% available drugs belong to the Biopharmaceutical Classification System (BCS) class II drugs which have poor aqueous solubility and low bioavailability. Hence, there is a constant need for the development in drug delivery methods which allows maximum therapeutic effectiveness. This can be achieved by drug encapsulation. Encapsulation of drug in the nano-sized polymeric particles can give minimal drug side effect, controlled drug release, and enhanced bioavailability (Langer, 1998).

In recent years, micro/nano materials have attracted the attention of many researchers towards their biomedical applications (Heath et al., 2016; Mitragotri et al., 2015; Tibbitt et al., 2016). Newly developed carriers hold great promise in accomplishing increased bioavailability, controlled drug release, and enhanced viability that can eventually achieve desired therapeutic response. Among these carriers, micro (Leong and Wang, 2015; Skorb and Möhwald, 2014) and nano (Gref et al., 1995; Wang et al., 2012) structures have gained considerable research interest because of their physical (size, structures, porosity, and mechanical strength) and chemical (compositions, reactivity, biocompatibility, and biodegradability) properties, and flexibility in integrating different functions. In particular, the nano drug delivery system provides a defensive impact against the degradation of drug, controlled therapeutic release profile, and the chance of accurately targeting the drug molecules to the specific site (Blanco et al., 2015). These advantages of nano drug delivery system enable the utilization of lower drug dose with minimal side effects as compared to bare drug molecules (Tang et al., 2016).

The two main methods for producing drug nanoparticles are top-down and bottom-up methods. In the top-down approach, large crystalline drug particles are converted to nanosized drug particles using mechanical force. These methods are easy for industrial scale-up with fine particle producing capacity and reproducibility. However, the major disadvantages of top-down approach are high equipment cost, uncontrolled particle growth, requirement of an intensive amount of energy, and a chance of product contamination (Gera et al., 2017). On the other hand, bottom-up approaches reduce drug particle size using the crystallization process. By using this approach usually, amorphous particles are produced thus enhancing solubility and bioavailability of the drug. However, amorphous form tends to re-agglomerate and has stability issues (Soliman et al., 2017). Bottom-up approaches are simple, rapid, energy efficient, and cost-effective (Azad et al., 2014). These techniques are more efficient at the laboratory scale, and smaller particle size with narrow particle size distribution can be achieved using these methods. The single step bottom-up approaches also have some disadvantages such as low yield, batch-to-batch variation, scaling up, and uncontrolled growth of particles. Nowadays, to produce drug nanoparticles with desirable properties, various combination approaches have been widely studied. In general, a combination technique involves a preprocessing step with a subsequent high energy step. Each approach has its advantages and disadvantages with a common aim of producing particles with good physicochemical stability, narrow particle size distribution, controlled particle growth, high purity, reproducible size, and desired morphology (Möschwitzer, 2010).

The emergence of microreactor technology has brought many opportunities for preparing drug nanoparticles with controlled properties. Microfluidics is defined as the science and technology which deals with fluid flow within micron size channels (Whitesides, 2006). In this micron range, the fluid behavior is majorly affected by fluid viscosity rather than inertia, and high surface area to volume ratio provides quick heat and mass transfer (Zhang et al., 2016). Owing to miniaturization of fluidic environment and continuous mode of operation, microreactor technology offers improved controllability, reduced batch-to-batch variation, narrow particle size distribution, reduced reagent consumption, and high reproducibility. In comparison with conventional processes, these intrinsic properties make microreactor technology attractive for producing drug micro/nano particles. Also, microfluidics has unique characteristics of using pico-to-nanoliter of reagent, millisecond mixing time, real-time monitoring/imaging, and direct scale-up. These characteristics offer microreactor technology as a cost-effective and high throughput technology (Ran et al., 2017). In the last few years, studies on the combination of microfluidic with precipitation and emulsification for drug encapsulation have been reported. Bramosanti et al. (2017) encapsulated Ribavirin in PLGA nanoparticles using microfluidic assisted nanoprecipitation technique. Hydrodynamic flow focusing geometry was utilized to prepare sustained release formulation of Ribavirin. The study demonstrated the significance of microfluidics for enhancing drug encapsulation and to tightly control process parameters (Bramosanti et al., 2017). de Solorzano et al. (2016) investigated microchannel emulsification by encapsulating cyclosporine into PLGA nanoparticles.

The current review revisits three methodologies, viz., (spray drying, high pressure homogenization, and ultrasonication) popularly investigated for drug nanonization and encapsulation in past few years. The advantages and limitations of the aforesaid techniques are discussed along with state-of-the-art in these technologies. The existing challenges of these techniques and their solution through microfluidics are highlighted. The advancement made in the field of drug nanonization and encapsulation through microfluidic technology was reported. Furthermore, the future scope of combining droplet microfluidic emulsification and ultrasonication for drug nanonization and encapsulation was discussed.

2. Widely investigated techniques in drug delivery

2.1. *Spray drying*

Among various techniques utilized for drug nanoparticles preparation, spray drying is widely accepted as it is a simple, fast, reproducible and scalable technology. Spray drying is a continuous technique which consists of an atomizer and a hot drying gas stream to convert a liquid feed into powdered product. The liquid feed comprises of drug particles suspended in the polymeric melt which are dispersed through an atomizer into fine size droplets. Liquid feed can be suspension, emulsion, solution, paste, or slurry. Spray drying is considered as the most widely studied and accepted encapsulation techniques with the major advantage of producing dried product directly (Chandralekha et al., 2016). Waghulde et al. encapsulated vildagliptin into PLGA nanoparticles for preparing sustained release formulation using lab scale spray dryer. The encapsulation efficiency for all prepared formulation varied in range of $57.10 \pm 1.27\%$ to $76.44 \pm 0.81\%$. Particles showed spherical and smooth surface morphology. *In-vitro* dissolution study confirmed the sustained release formulation over a period of 12 h (Waghulde et al., 2018). Salazar-Miranda et al. investigated the combination of spray drying of double emulsion (SDE) in comparison with particles obtained from spray drying melt granulation coating method (MGC). Also, smaller particle size of 16 μm was obtained for SDE whereas,

700 μm particles were obtained from MGC method. Furthermore, particles prepared using both the techniques showed lower degradation (<2%), and higher solubility (>80% in 20 min) (Salazar-Miranda et al., 2016).

The process parameters involved for drug encapsulation through spray drying are flow rate and concentration of feed, applied pressure and voltage, type of atomizer, flowrate of hot air, and inlet and outlet temperatures. The morphology and density of the final dried product can be tailored by Peclet number (Pe), which is the ratio of droplet evaporation rate and the diffusional motion of solutes. Castro et al. investigated soy protein isolate (SPI) and acylated soy protein (SPA) as an encapsulating carrier for oral pharmaceutical applications. Ibuprofen was encapsulated in SPI and SPA through spray drying. Fig. 1 shows the SEM images of prepared microparticles of SPI and SPA at different drug to carrier ratio. An uneven shrinkage of microparticles was reported due to drying and/or cooling step. For spray dried particles wrinkled surface morphology was observed with high protein content. The internal structure showed no evident porosity in matrix. Furthermore, no free drug particles were observed even at high ibuprofen encapsulation rate (Castro et al., 2018).

One of the classical approaches of spray drying technique is that it can be used for heat sensitive and heat resilient as well as water soluble and water insoluble drugs. However, product quality of thermally sensitive materials may get degraded easily at normal conditions. Hence, to overcome this issue it is suggested to use multiple stage dryer. Behboudi-Jobbehdar et al. (2013) tried to encapsulate temperature sensitive probiotic lactobacilli strains lactobacillus acidophilus stabilized in maltodextrin. Results showed acceptable thermo physical properties and low inactivation rate during storage at room temperature. The preparation of drug loaded nanoparticles using this approach enables stable particles with higher encapsulation efficiency. Zernov et al. (2017) reported B-90 Buchi nano spray dryer by piezoelectric spray drying as a high-tech scalable method for encapsulating paclitaxel in poly(3-hydroxybutyrate). Despite numerous advantages, spray drying approach has difficulties like low product yield, sticking or high moisture content in product. Generally, low yield is due to loss of product on the walls of drying chamber which is also responsible for high maintenance cost. In addition, it is difficult to collect particles with size less than 2 μm due to ineffective separation capacity of cyclone (Maury et al., 2005; Stahl et al., 2002). Oliveira et al. (2013) reported that nanoparticles produced using spray drying technique tends to agglomerate during process resulting in sub-micron to micron size particles. Some of the recent literature findings on drug nanonization and encapsulation through spray drying are reported in Table 1.

2.2. *High pressure homogenization (HPH)*

A mechanical process that subdivides particles or droplets into micron size to form a stable dispersion or emulsion is HPH. The mixture is subjected to high pressure of 100–2000 bar, shear stress, and turbulence, resulting in disruption of particles. This process enhances drug stability and shelf life. The design of special homogenization valve is the heart of this process where reaction occurs. The fluid passes through a small orifice which causes high turbulence and shear, combined with compression, acceleration, and pressure drop. When pressure drop is large enough, the vapor pressure on the liquid surpasses the ambient pressure initiating creation of vapor bubbles or cavities in liquid. The generated cavities collapse, shock waves are generated in liquid that ultimately results in generating finely scattered emulsion. Using HPH technique, Levet et al. developed cisplatin submicron size particles stabilized with lipid and/or PEGylated component. To obtain dry powder for inhalation (DPI) for lung cancer treatment spray drying technique was used to produce controlled release formulation. DPI showed high dispersion properties, high drug loading and *in-vitro* lung deposition. With limited burst release profile, controlled release profile over 24 h in lung fluid simulated media was obtained. Hence, effectiveness of combining HSH, HPH, and spray drying technique to produce DPI formulation was demonstrated (Levet et al., 2016).

Recently, Zhou et al. performed a comparative study between amphotericin B (AmB) nanosuspension prepared through HPH and antisolvent precipitation (AP) method. Particles with irregular shape and 200 nm size were obtained through AmB-HPH whereas, particles with spherical shape and 60 nm size were prepared through antisolvent precipitation approach. TEM images showing the surface morphology of AmB-HPH and AmB-AP are shown in Fig. 2(a). The irregular surface of particles prepared using HPH was attributed to the shockwaves of high pressure homogenization and drug hardness. The release curve for AmB, AmB-HPH, and AmB-AP along with plasma concentration time curve after oral administration of reference formulation to rats is shown in Fig. 2(b). A greater saturation solubility and dissolution rate was observed for AmB-AP then that of AmB-HPH. However, higher relative bioavailability due to better stability was obtained for AmB-HPH (Zhou et al., 2018).

Park et al. successfully encapsulated vitamin D3 (VD3) in nanostructured lipid carriers (NLCs) by HPH. The VD3-NLCs obtained from 10 cycle of hot HPH at 10,000 psi showed particle size of 132.9 nm, PDI 0.19, and zeta potential −41.90 mV representing particles stability and resistance to agglomeration. A high EE of 85.6% with controlled release profile and stability for 20 days evaluation period was observed. They concluded that NPs prepared using HPH could be effectively applied for encapsulating and increasing the oral bioavailability (Park et al., 2017). HPH generally uses either water or a non-aqueous medium for operation. The production of drug NPs without using any organic solvent is a major advantage of this technique. Moreover, features like capacity to handle very dilute to highly concentrated suspension, high drug loading and EE, and scale up feasibility makes this technology attractive and widely studied. However, high equipment cost, large number of homogenization cycles, and prerequisite of drug being in micro size before homogenization are hurdles in its implementation. Table 2 represents the examples of drug and techniques used in combination with HPH.

2.3. *Ultrasound*

Another approach widely investigated to encapsulate drug and to nano size drug is ultrasonication. The ultrasonic energy can be introduced in a system by dipping a probe sonicator in a vessel or putting the vessel in a bath sonicator. When sound waves are introduced, bubbles are generated at liquid–liquid interphase which are also known as cavities, and simultaneously bubbles collapse which releases shock waves. The waves results in rapid mixing, reduced particle size, faster primary nucleation (Xia et al., 2010). The particle size depends on sonication amplitude, frequency, horn length and diameter, and sonication time. By strictly controlling the process

Table 1 – Literatures reported for drug encapsulation and nanonization through spray drying.

API/drug	Agent	Motive	Results							Remark/s	Reference
			EE	Yield	DR	PS	Morphology	PDI	ZP		
Rifampcin	Dextrans 40 and 70	Dry powder inhaler for enhanced lung delivery	100	–	–	5000	Spherical	–	–	Better inhalation properties	Kadota et al. (2019)
Doripenem	Chitosan	Controlled pulmonary delivery	78.98	74.03–98.23	72.34 in 1 h	3800–6900	Spherical and corrugated	–	−0.36	70–90% cell viability	Yildiz-Peköz et al. (2018)
Vildagliptin (VLG)	PLGA 50:50, PLGA 75:25, and PDLA	Sustained release	57.10–76.44	47.2–62	94.82 in h	428	Spherical	0.22	–	PLGA 50:50 showed highest encapsulation	Waghulde et al. (2018)
Metformin hydrochloride (MF)	Alginate (ALG) cross-linking by $CaCl_2$	Sustained release	93.9	56.1	97.5 in 12 h	3400	–	–	2.6	Improve mucoadhesive properties and decrease swelling ratio	Szekalska et al. (2018)
Ibuprofen	Soy protein isolate (SPI) and acylated soy protein (SPA)	Delayed release	80	70–87	28 in 1 h for SPA and 42.8 in 1 h for SPI	1000–9000	Spherical with uneven shrinkage and wrinkle	–	–	pH sensitive DR with delayed release in simulated gastric fluid and rapid and complete release in simulated intestinal fluid	Castro et al. (2018)
Flutamide	Ocimum Basilicum Mucilage (OBM)	Enhance bioavailability for rectal drug delivery	69.6	6.66–17.91	88.7 at 7 h	2530	Spherical	–	−40 to 20	89.01% mucoadhesion	Ige et al. (2018)
3-Nitro-2-hydroxi-4,6-dimethoxychalcone (CH8)	PLGA (lactide-glycolide molar ratio of 50:50)	To enhance drug loading	–	–	–	1500–2600	Spherical	–	–	Drug loading of 18% w/w was achieved	Sousa-Batista et al. (2018)

Table 1 (*Continued*)

API/drug	Agent	Motive	Results							Remark/s	Reference
			EE	Yield	DR	PS	Morphology	PDI	ZP		
Famotidine (FMT)	2-HydroxyPropyl-β-cyclodextrin (HP-β-CyD) and Polyvinylpyrrolidone K-30 (PVP K-30)	Solubility enhancement	92.1	–	98.49% in 20 min	164–300 and 1000–2600	Spherical	–	–	Fast dissolving tablet showed 38-fold solubility enhancement	Verma et al. (2017)
Sildenafil	PLGA (Resomer RG502H, Resomer RG502, and PLGA5010)	Sustained release	90	Greater than 68%	Sustained release from 4 to 12 h	4000–8000	Spherical	–	–	Vibrational spray dryer replaced by fluid atomizer for scale-up	Beck-Broichsitter et al. (2017)
Cefquinome	PLGA	Sustained release for intravenous administration	91.6	–	24.2 in 1 h followed by sustained release for 48 h	12,400	Spherical	–	–	Targeted drug delivery 18.3 drug loading	Qu et al. (2017)
Paclitaxel	Poly(3-hydroxybutyrate) (PHB)	Sustained release	–	–	Prolonged release up to 100 days	7860	Spherical	–	−42	Comparison with direct membrane emulsification method	Zernov et al. (2017)
Atorvastatin calcium (ATV)	Pectin, Alginate, Chitosan HCl, and Hydroxy propylmethyl cellulose (HPMC)	Enhance dissolution rate for antihyperlipidemic effect	–	30–46.82	100 in 30 min	4530	Spherical with shallow dents	–	–	Moisture content-4.8–5.6% Pectin suitable polymer with 3% w/w	Basha et al. (2017)
Amodiaquine	Bovine Serum Albumin powder (BSA)	Sustain drug release	91.35	–	93 in 24 h	2400	Irregular and porous	–	−25.5	1.8-fold increment in relative bioavailability	Nettey et al. (2017)

Table 1 (*Continued*)

API/drug	Agent	Motive	Results							Remark/s	Reference
			EE	Yield	DR	PS	Morphology	PDI	ZP		
Isoniazid (INH)	Eudragit S100, Eudragit L100-SS based co-processed Acryl EZE (EZE), Ethyl cellulose (ECN10)	Controlled release	81–94.4	63–82	Burst release for 2 h followed by sustained release for 12 h	Less than 10,000	Spherical	–	–	22.8–45.1 drug loading	Mithu et al. (2017)
Artemisinin (ART) and Mefloquine (MFQ)	Mesoporous silica (SBA-15)	Solubility enhancement	–	–	95 in 30 min	500–1000	Spherical and spheroid	–	–	2-fold higher stable super-saturation	Letchmanan et al. (2017)
Azithromycin (A)	Eudragit E100 (E), polyethylene glycol (PEG) 4000	Controlled release	–	–	70 in 6 h at pH 1.7 and 35–40 in 6 h at 7.4	2000	Spherical	–	–	Best coating condition- 3:2:1 of E: PEG: A at pH 6	Hamzehloo et al. (2017)
Diclofenac sodium (DS)	Eudragit RS-100, Ethyl cellulose	Sustained drug delivery	69.12	–	Up to 70% in 12 h	2000–12,000	Spherical	–	–	Fickian release dominant mechanism for DR	Deshmukh and Naik (2016)
Mefenamic acid	Ethyl cellulose, Eudragit RL-100	Sustained drug delivery	83.73–96.69	–	98.98 in 12 h	6550–41,100	Round	–	–	Solvent evaporation approach was also studied	Wagh and Naik (2016)
Metformin hydrochloride (MH)	Ethyl cellulose	Sustained drug release	–	–	77.73–96.27	400–700	Smooth and regular	–	–	54.48–77.8 Drug loading	Mokale et al. (2016)

EE: encapsulation efficiency (%), DR: drug release (%), PS: particle size (nm), PDI: polydispersity index, ZP: zeta potential (mV).

Table 2 – Literature reported on combination of various approaches with HPH in drug delivery.

API/drug	Agent	Combination technique	Motive	Results						Remark/s	Reference
				EE	DR	PS	Morphology	PDI	ZP		
Nimodipine (NMP)	Precirol ATO 5, and Glyceryl monostearate (GMC), Poloxamer 188, Tween-80, Polyoxyethylene ester of 12-hydroxy steric acid (Solutol HS-15), Polyoxyethylene castor oil (ELP), Hydrogenated polyoxyethylene castor oil (RH 40), and Vitamin E polyethylene glycol succinate (TPGS)	Oil-in-water emulsion	To enhance solubility and bioavailability	86.8	29.77 in 49 h at 6.8 pH and 20 in 48 h at 1.2 pH	71	Spherical	0.057	−23.8	Tween-80 showed highest EE and PS NPs were stable for 2 weeks at 4 °C and 25 °C and more suitable condition was suggested at 4 °C. 160.96% enhancement in relative bioavailability	Teng et al. (2019)
Dibucaine (DBC)	Myristyl myristate (MM), Cetyl palmitate (CP) and Pluronics F-68	Hot–melt emulsification	Prolonged drug release and reduce its toxicity	72.3–89.3	Initial burst release followed by sustained release for 48 h	188–288	Spherical	0.14–0.27	−3 to −45	Stability study for 240 days Comparison with tip US Average diameter of NPs through HPH was slightly smaller than US PDI value was significantly smaller for HPH	de M Barbosa et al. (2018)

Table 2 (*Continued*)

API/drug	Agent	Combination technique	Motive	Results						Remark/s	Reference
				EE	DR	PS	Morphology	PDI	ZP		
Andrographolide (AG)	Cremophor, α-topherol, triacetine, limonene, Tween 80, Tween 20, and Span 80	Oil-in-water emulsion	To enhance solubility, intestinal penetration and stability	95.7	–	122	Round and smooth	0.016	–	Drug loading-0.3% Relative bioavailability of NPs-594.3% Jejunum optimum site for AG absorption	Yen et al. (2018)
Vitexin	Poloxamers 188	Antisolvent Precipitation	To enhance dissolution rate	–	96.58 in 30 min	80.9	Spherical	–	−18.5	5.58-fold enhancement in solubility Residual DMSO was lowered than ICH limit	Gu et al. (2017)
Voriconazole (Vrc)	Miglyol 812N, Compritol 888 ATO, Gelucire 44/14, Solutol HS 15, and Tween-80.	Oil-in-water emulsion	To enhance antifungal activity and drug delivery efficiency	75.37	–	45.62	Spheroid	0.18	−0.69	NPs were stable for 4 weeks at 4 °C Drug loading-3.77%	Tian et al. (2017)
Sipronolactone (SPI), Nifedipine (NI)	Monoolein cubosomes and Pluronic F-127	Solid dispersion	To enhance solubility and bioavailability	90.2 for SPI and 93 for NI	5 in 12–48 h	90.4 for SPI and 91.3 for NI	–	0.187 for SPI and 0.168 for NI	−13.4 for SPI and −12.8 for NI	6-fold enhancement in SPI solubility and 9-fold enhancement in NI solubility Size and PDI was stable for 4 weeks	Ali et al. (2017)
Paclitaxel (PTX)	Hyaluronan (HA), Polysorbate 80, soybean oil, and DL-α-tocopheryl acetate	Emulsification	To enhance antitumor efficacy	100.1	60 in 6 days	80.3	Spherical	0.20	−36.9	Tumor growth was highly suppressed and reduction in toxicity was observed	Kim and Park (2017)

Table 2 (*Continued*)

API/drug	Agent	Combination technique	Motive	Results						Remark/s	Reference
				EE	DR	PS	Morphology	PDI	ZP		
									Drug loading-3.69	Retention time and accumulation of PTZ in cancer cells increased	
Clopidogrel	Pluronic F127	High speed homogenization	To enhance bioavailability	99.11	98.37 in 0.1 N HCl and 48.67 in 6.8 pH within 2 h	478.1	–	0.730	−6.61	A 2-fold improvement in 0.1 N HCl and 10-fold enhancement in 6.8 pH for solubility was observed	Qureshia et al. (2017)
Tamoxifen	Human serum albumin (HSA)	Emulsification	To develop homogenization processes (HPH and HSH) for preparing protein NPs	95.15	–	156.2	Semi spherical	0.152	−19.9	For HSH PS-134.1 PDI-0.111 ZP-−14.8 EE-87.3 DL-11.6 was obtained.	Safavi et al. (2017)
10-Hydroxy-camptothecin (10-HCPT)	Poloxamer 188 (used as cryoprotective agent)	Acid–base microprecipitation	To prepare stabilizer and solvent free NPs	–	95.6 in 5 h	133.5	Spherical	0.13	−27	In-vivo study revealed smaller tumor volumes Drug loading-75% Higher cellular up take and plasma concentration	Yang et al. (2016)

Table 2 (*Continued*)

API/drug	Agent	Combination technique	Motive	Results						Remark/s	Reference
				EE	DR	PS	Morphology	PDI	ZP		
Linalool (LL)	Glycerine mono stearate (GMS), Decanoyl/octanoyl–glycerides (MCT), Tween 80 and Span 80	Hot–melt emulsification	To reduce volatilization and increase bioavailability	79.563	15.564 in 180 min	52.72	Spherical	0.172	−16	Optimization through central composite design Drug loading-7.555% In-vivo pharmacokinetics study revealed 393.34% relative bioavailability	Shi et al. (2016)
Paclitaxel (PTX) and Curcumin (CCM)	Bovine Serum albumin (BSA)	Water-in-oil-water emulsification	Co-loading PTX and CCM for prominent anticancer efficacy	–	97.7 PTX and 76.2 CCM over 24 h	250.4	Spherical	–	−29.8	Enhanced cytotoxicity due to combined effect Drug loading-96.5% for PTX and 88.6% for CCM	Kim et al. (2016)

EE: encapsulation efficiency (%), DR: drug release (%), PS: particle size (nm), PDI: polydispersity index, ZP: zeta potential (mV), ICH: international conference on harmonization.

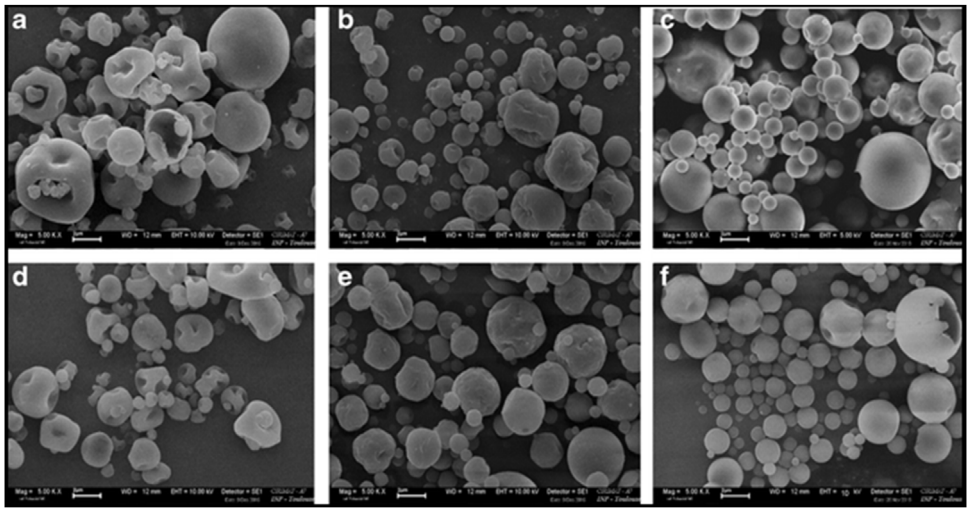

Fig. 1 – Scanning electron micrograph of microparticles. (a) SPI microparticles (b) SPI/IBU 80/20 (c) SPI/IBU 60/40 (d) SPA (e) SPA/IBU 80/20 (f) SPA/IBU 60/40, magnification of ×50000, scale bars 2 μm. Reproduced from (Castro et al., 2018) with permission of Springer Nature.

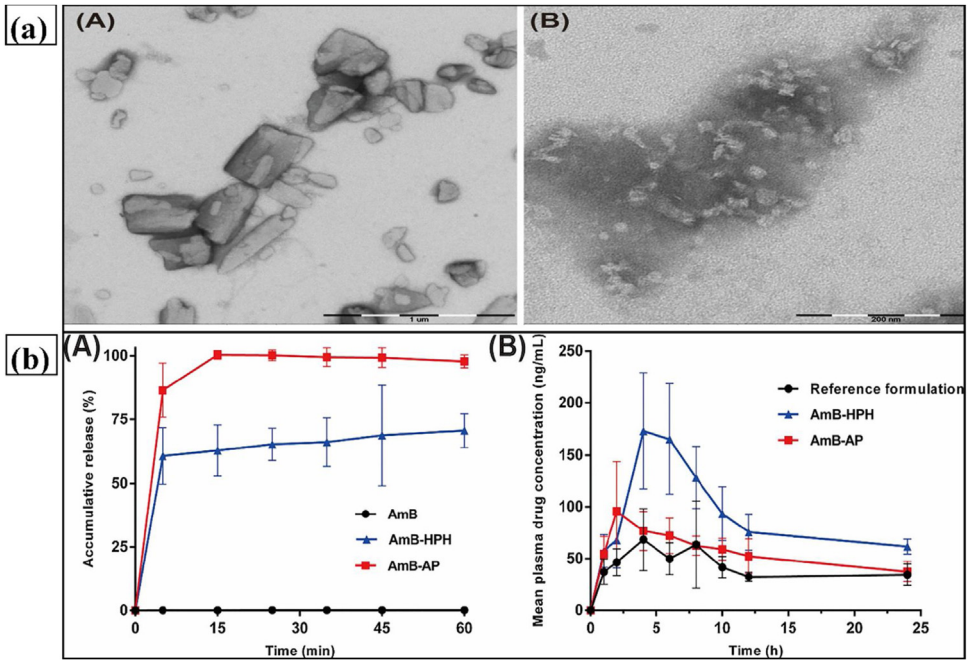

Fig. 2 – (a) TEM images of (A) AmB-HPH and (B) AmB-AP. (b) (A) Release curve of AmB, AmB-HPH, and AmB-AP in PBS (B) Plasma concentration time curve after oral administration of reference formulation to rats at dose of 10 mg/kg. Adapted from (Zhou et al., 2018) with permission of Elsevier.

parameters, it is possible to achieve nano range particles. Nemati et al. investigated the combination of hot homogenization with ultrasonication to prepare ethambutol hydrochloride (EMB) loaded solid lipid nanoparticles for pulmonary drug delivery. The encapsulation efficiency higher than 98% was achieved. Spray drying was employed to obtain dry powder inhaler (DPI) of EMB loaded solid lipid nanoparticles (SLNs) with and without mannitol. Results revealed the flowability of prepared powder, biocompatibility and non-toxicity of SLNs (Nemati et al., 2019).

Rahim et al. studied simple and cost-effective ultrasound assisted precipitation approach to enhance solubility, oral bioavailability, and analgesic potential of aceclofenac. The drug nanoparticles with 112 ± 2.01 nm and 0.165 PDI were produced at optimum conditions. At ultrasonic input of 200 W and processing time of 15 min at pause of 3 s, the batch size of 400 mL was suggested for scale up (Rahim et al., 2017). The major drawback of this batch process includes difficulties in its scale up and high batch-to-batch variation. Moreover, Dalvi and Dave reported that if the ultrasound energy is supplied beyond a critical value, it imparts high kinetic energy to the particles, resulting in greater particle collisions and agglomeration (Dalvi and Dave, 2009). Table 3 presents the example of research work on combination of various techniques with ultrasound for drug encapsulation and size reduction. Sharma et al. studied the impact of sonication time on particle morphology in ultrasound assisted antisolvent crystallization. Fig. 3 shows the SEM images of raw telmisartan and recrystallized telmisartan. The raw drug particles had acicular shape and edges were slightly round with size in 4–10 μm range. For recrystallized drug the particle size reduced to 200–400 nm at 10 min and 15 min sonication time. Results showed nee-

Table 3 – Examples of research work on combination of various techniques with ultrasound for drug encapsulation and size reduction.

API/drug	Agent	Combination technique	Motive	Results						Remark/s	Reference
				EE	DR	PS	Morphology	PDI	ZP		
Griseofulvin (GF) and sulfamethoxazole (SMZ)	Carboxylated carbon nanotubes (CNTs)	Antisolvent precipitation	Solubility enhancement	–	80% dissolution in 18 min for GF and 10 min for SMZ	–	Rod shape	–	–	4% incorporation of CNTs in GF and 5.1% incorporation of CNTs in SMZ	Chen and Mitra (2019)
Telmisartan	Surfactant-SLS and Tween-80 Polymer- PVP k-30, PVP k-90, PEG 6000, HPMC	Antisolvent precipitation	To enhance solubility and study effect of polymer and surfactant	–	–	186.9 for Tween-80 and 165.2 for PVP k-30	Acicular for surfactant and rod shaped for polymer	–	−1.54 to 3.24 for surfactants and −1.24 to −12.16 for polymer	Best suitable surfactant and polymer obtained were Tween-80 and PVP k-30	Sharma et al. (2019)
Baicalin	Carboxymethyl chitosan (CMCS), Poloxamer 407 (F127), Genipin (GP), Compritol 888 ATO, Miglycol 812 N, Cremophor EL, and Soy lecithin	Melt-emulsification	Prolonged ocular delivery	89.05	81.1% in 10 h	99.6	Spherical	0.24	–	4.46-fold greater permeability coefficient No irritation to cornea	Yu et al. (2018)
Curcumin	Sodium dodecyl sulfate (SDS), HPMC, Tween 80, Bovine serum albumin (BSA)	Antisolvent precipitation	Solubility enhancement	–	–	2000–4000	Orthorhombic	–	–	Best polymer HPMC Monoclinic form of curcumin 100 times lowered mixing time	Pandey et al. (2018)

Table 3 (*Continued*)

API/drug	Agent	Combination technique	Motive	Results						Remark/s	Reference
				EE	DR	PS	Morphology	PDI	ZP		
Loratadine	HPMC, PVP K-25, Poloxamer 188, tween 80, SLS, Pluronic F68	Antisolvent precipitation	Solubility and bioavailability enhancement	–	30–42% 10 min	353–441	Rod shape	0.167–0.229	−25.7 to −20.7	Pluronic F68 with 0.2% concentration showed best results	Alshweiat et al. (2018)
Methylprednisolone (MP)	Span 80, Precirol ATO 5, Tween 20	Emulsification and High speed homogenizer	Maximize drug availability at target site	48.9	43.2% in 96 h	76.7	Spherical	0.231	−26.7	Viscosity of gel- 88205 cP	Xiao et al. (2018)
Paclitaxel (PTX) and NuBCP-9	PLA-(PEG-PPG-PEG)]	Emulsification	Improve antitumor activity and reduce chemo toxicity	99.19 for PTX and 28.77 for NuBCP-9	~47% in 7 days	160.1	Spherical	0.07	−11.3	NPs inhibited growth and survival of breast carcinoma cells	Gupta et al. (2018)
Nevirapine	Cellulose Acetate Butyrate (CAB), and PVA	Emulsification	Macrophage targeted drug delivery	75.89	54.41	305.76	Spherical	0.29	−6.8	Improved bio-compatibiliy and cellular uptake in macrophage cell lines	Varshosaz et al. (2018)
Telmisartan	–	Antisolvent precipitation	To enhance solubility	–	–	200	Rod or needle like structure	–	–	Probe sonication with 13 mm diameter was used to study the effect of process parameters on PS and surface morphology	Sharma et al. (2018)
Efavirenz (EFV)	HPMC, PVP K-30, Lutrol F 68, SLS, and Lutrol F127	Antisolvent precipitation	Solubility and bioavailability enhancement	–	80% in 60 min	176.8–4234	Elongated particles with film formation	0.320	−29.5	Suitable polymer HPMC and PVP K-30	Sartori et al. (2017)
Prednisolone	Zein	Antisolvent precipitation	Solubility enhancement	–	92% 60 min	–	–	–	–	D:P-1:2 S:AS-3:10	Nguyen et al. (2017)
Lacidipine (LCDP)	Pluronic F127, sodium deoxycholate (SDC), PVA	Antisolvent precipitation	Solubility and bioavailability enhancement	–	100% 120 min	273.21	Nearly spherical	0.098	−32.68	70-time solubility enhancement	Kassem et al. (2017)

Table 3 (*Continued*)

API/drug	Agent	Combination technique	Motive	Results						Remark/s	Reference
				EE	DR	PS	Morphology	PDI	ZP		
Naringenin (NRG)	PVP K-30, HPMC E5, Tween 80, Pluronic F68	Antisolvent precipitation	Solubility and bioavailability enhancement	–	91% in 60 min	117	Spherical	0.153	−14.6	Best results with PVP K-30, 0.5% w/v Cmax and AUC0-24 h 2 and 1.8-fold greater	Gera et al. (2017)
Carboplatin	Polycaprolactone (PCL)	High speed homogenization and Emulsification	Sustained drug release	27.95	Burst release followed by sustained release	311.6	Spherical	0.21	−16.3	Better permeation and nasal absorption	Alex et al. (2016)
Prednisolone	PLGA	HSH and emulsification	Ocular bioavailability enhancement	60–92%	Prolonged release	294.5	Spherical	0.081	5.6	Contact lens showed improved wettability, and decreased hydration	ElShaer et al. (2016)
Cinnarizine	PVA	Antisolvent precipitation	Solubility and bioavailability enhancement	–	90% in 7.09 min	636.78	Spherical	–	−26.15	2.7-fold enhancement in oral bioavailability	Mishra et al. (2016)
Candesertan cilextil	Compritol 888 ATO, high shear homogenization	o/w emulsion, high speed homogenization	Solubility and bioavailability enhancement	100	24.1%–50.8% in 30 days	90.7–1382	Spherical	0.323–0.834	−19.5 to −31.5	D: lipid-1:30 Surfactant: cosurfactant-1:2 Combination technique found successful	Ugurlu et al. (2016)
Isradipine	Polyethylene oxide N-60K (PEO), HPMC 6 cps, HPMC 4000 cps	Antisolvent precipitation	Solubility enhancement	–	100% in 120 min	50	More uniform	–	–	Best polymer: HPMC 6 D:P ratio- 1:1	Tran et al. (2014)

EE: encapsulation efficiency (%), DR: drug release (%), PS: particle size (nm), PDI: polydispersity index, ZP: zeta potential (mV).

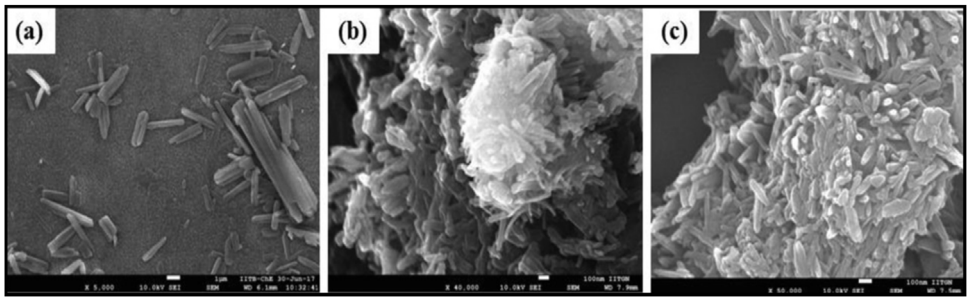

Fig. 3 – SEM image (a) Raw telmisartan, and recrystallized telmisartan drug sample obtained by varying sonication time at (b) sonication time of 10 min, and (c) sonication time of 15 min. Reproduced from Sharma et al. (2018) with permission of John Wiley and Sons.

Table 4 – Advantages and disadvantages of widely studied technique in drug delivery.

Technique	Process parameters	Advantages	Disadvantages
Spray Drying	• Feed flow rate • Nozzle diameter • Hot air flow rate • Feed inlet and outlet temperature • Atomization gas type	• Simple and single step process • Cost-effective • No need for particle separation • Can be scaled up • Good aerosolization	• Low yield (~50%) • Not suitable for heat sensitive materials • High maintenance • High moisture content in the product • High energy and pressure requirement
High pressure homogenization	• Volumetric flow rate • Valve geometry • Temperature • No. of homogenization cycle	• High encapsulation efficiency • High reproducibility • Smaller particle size and particle size distribution • Organic solvent free method	• Energy intensive process • High temperature process • Possible product degradation
Ultrasonication	• Amplitude • Frequency • Temperature • Sonication time	• Fast primary nucleation • Reduced shear stress • Low operational cost • Process intensification • Smaller particle size	• Particle agglomeration • Physical instability upon storage • Difficulty in scale up • Broad particle size distribution
Microreactor	• Feed flow rate • Microchannel diameter • Microchannel length • Temperature • Micromixer geometry	• High encapsulation efficiency • Good reproducibility • Continuous process • Short residence time and minimal reagent consumption • Smaller particle size and narrow particle size distribution • Easily scalable • Tight control over process parameters	• Susceptibility of clogging • Processing of solids

dle like shaped particles with regularly shaped crystals, which are agglomerated (Sharma et al., 2018). In addition, advantages and disadvantages of widely studied techniques in drug delivery are reported in Table 4.

3. Microreactor

In the past few years, microfluidic technology has grown rapidly with extensive applications in preparing nanoparticles, and to carry out various chemical reactions. Microreactor is a device where the reaction takes place in channels with an inner diameter less than 1 mm. The smaller channel dimensions enhance the surface area to volume ratio resulting in higher heat and mass transfer. When compared with conventional batch reactors, this technology offers precise control of process variables (temperature, concentration, and reaction time). High surface area to volume ratio and mixing characteristics provide temperature and concentration homogeneities, monodispersed nanoparticles, reproducible composition, structure, and physicochemical properties. Because of all these characteristics, microreactor technology is now being considered as the technology of choice for producing nanoparticles (de Solorzano et al., 2016).

A simple microreactor system involves a pump, micromixer followed by tube or channels (with an inner diameter in micron range), and quench zone as shown in Fig. 4. For continuous operation, a reliable pump like a syringe pump, high-performance liquid chromatography (HPLC) pump, or a peristaltic pump can be used. First preference for small scale systems is the syringe pump. Precise and constant flow rate can be achieved through a syringe pump over several order of magnitude. However, smaller capacity (<500 mL) results in a frequent refill of the syringe. HPLC pumps are operated at high pressure and provide higher flowrate than

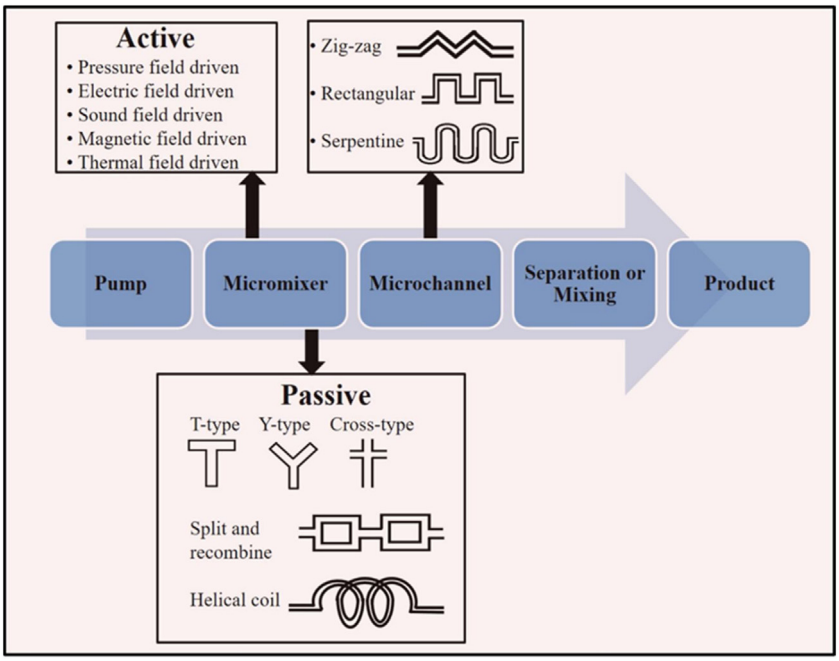

Fig. 4 – A schematic representation of a typical microreactor system.

syringe pumps. But, HPLC pumps cannot be used for viscous fluids which cause failure in the check valve. The peristaltic pump can be used to handle viscous, slurries, and shear sensitive fluids. At low flowrate the flow is pulsed therefore, this pump is not suitable when a precise and constant flow is required.

One of the most important components of a microreactor system is the micromixer which has a significant impact on the sensitivity and efficiency of the microfluidic system. To efficiently mix reagent streams and to rapidly achieve a single well-mixed stream micromixer are used. Micromixers are broadly classified as active and passive micromixers. In active micromixer, different external energy sources are applied to create disturbance in fluid flow, to increase the contact area, or to induce chaotic advection and thus enhancing mixing performance. Based on the type of external energy source, active micromixers are classified as pressure field driven, electric field driven, sound field driven, magnetic field driven, and thermal field driven micromixers (Cai et al., 2017). Kamat et al. (2015) reported the synthesis of chitosan nanoparticles using a polydimethylsiloxane (PDMS) microfluidic device containing magnetic microneedle for active synthesis. Rhombic shape microneedle of 0.5 mm length was utilised to have maximum confluence while mixing. In passive micromixer, the geometry of micromixer is used to create turbulence and chaotic advection for efficient mixing. The widely used micromixers are passive micromixer. Based on mixing structures, the most common type of passive micromixers are simple contacting structures, split and recombine structure, helical or curved structures, and multi-lamination structures (Zhang et al., 2017). T-type micromixer, Y-type, and cross micromixer come under the category of simple contacting structures. By changing the orientation of connecting streams, different fluid flow dynamics and mixing efficiency are obtained. Although, these micromixers are simple to fabricate and use, they have poor performance in case of multiphase flow. de Solorzano et al. studied three types of passive micromixers (T-type, Y-type, and cross micromixer) by varying mixing time from 20 to 10 ms. Highly polydispersed particles were produced using Y-type micromixer. However, enhanced mixing and narrow particle size distribution was observed when the configuration was T- type. The best results were obtained at the cross micromixer unit (de Solorzano et al., 2016). Majedi et al. reported the preparation of paclitaxel loaded chitosan nanoparticles using a T-type microfluidic device. The particle size of 100 nm with high drug loading and sustained release was achieved (Majedi et al., 2014). Split and recombine micromixers continuously stretch, cut, and stack the fluid streams to enhance mixing. These types of micromixers are excellent in case of highly viscous fluid and multiphase fluids. Nevertheless, high pressure drop is a limitation of this micromixer. Helical or curved structure micromixer at high flow rates generate chaotic advection, thus enhancing the mixing efficiency. These are easy to fabricate however are not suitable for low flow rates.

Furthermore, multilamination structures generally use multiple layer structures for achieving excellent mixing performance within milliseconds. These micromixers are based on shear thinning fluids into films and are costly to fabricate. Due to their small length for diffusion, these can give high mixing efficiency at low flow rates. Micromixers are generally followed by microchannel to provide enough residence time for the reaction to proceed. By controlling the length of microchannel, the fluid residence time can be easily tuned (Adamo et al., 2016). Microchannel can have a coil, zig-zag, rectangular, and serpentine structures with channels of polymer or steel. The integration of micromixer with microchannel gives small compact volume systems (Woitalka et al., 2014). Patil et al. used serpentine mannered silicon tube to encapsulate ketorolac tromethamine in chitosan nanoparticles. Spherical particles with encapsulation efficiency between 76–96% showed sustain drug release over 12 h (Patil et al., 2019). Advanced microreactor system often combines various mixing design structure into one device.

Several materials have been applied to fabricate microfluidic devices, and each has its advantages and disadvantages. The fabrication material can influence the surface characteristics of the microchannel, the prevalence of fouling

and clogging within the microchannel, and heat transfer. The selection of appropriate fabrication material depends on operating conditions such as pressure and temperature, compatibility with solvent and solute, physical properties of solute and solvent (pH and viscosity), cost, and ease of fabrication. Generally, materials used to fabricate microfluidic devices can be classified into three classes (i) inorganic materials (glass and silicon), (ii) elastomers and plastics (PDMS, PMMA, PVC, and PLA), (iii) hybrid and composite materials (PDMS/glass) (Ren et al., 2013). Silicon is widely available, relatively inexpensive, resistant to organic solvents, optically transparent, easy for surface modification, and highly biologically compatible thus, is extensively used in microfluidic device fabrication (Pollack et al., 2002). Wagh et al.(2019) fabricated microfluidic reactor using silicon tube of 0.8 mm ID and 183 cm microchannel length for drug encapsulation in ethyl cellulose. The silicon microfluidic device can achieve excellent laminar flow even in case of an interfacial reaction. However, silicon is fragile, has complex surface chemistry, and is fabricated using expensive techniques which are major hurdles in its application. PDMS, another frequently used material is inexpensive, has good permeability, and optical property which makes it popular fabricating material (Longuet et al., 2014). However, the poor compatibility with organic solvents is a drawback of PDMS. Glass as a fabricating material has the advantage of flow visualization, and capability to withstand high operating pressure but, has difficulty in creating high aspect ratio structures (Suryawanshi et al., 2018). Polymethyl methacrylate (PMMA) has also been used to fabricate thermoplastic microfluidic system. Muck et al. reported a simple, user-friendly, and effective method for fabricating PMMA microfluidic device using atmospheric moulding (Muck et al., 2004). PMMA offers the benefits of high optical transmission, excellent solvent compatibility, high stability, and easy fabrication (Tsao and DeVoe, 2009). Despite these benefits, application of PMMA is limited as long-term exposure of organic solvent on PMMA channels create swelling and rupture resulting in deformation of rough surfaces. Nowadays, fabrication of microfluidic device through a combination of materials is a subject of on-going research. By using hybrid and composite materials, improved functionality of the microfluidic device can be achieved. Yu et al. (2012) utilised the combination of PDMS and glass to fabricate microfluidic device for protein crystallization.

3.1. *Microfluidics for drug delivery*

In general, much of the drug nanoparticles are prepared using batch approaches. In conventional batch operation, precursors are mixed through convection, stirring, and shaking etc. and particles are prepared using precipitation, emulsion, and sol–gel methods. The gradually changed solvent to the anti-solvent ratio in bulk synthesis results in the heterogeneous environment leading to formation of polydispersed particles. Moreover, conventional approaches lack in precisely controlling the mixing process which results in aggregated particles. During the preparation of drug nanoparticles through these approaches; nucleation, growth, and agglomeration occurs simultaneously. The lack of control over these processes shows high batch-to-batch variation in physicochemical properties of particles like size distribution, average particle size, surface charge, and drug release profile (Choi et al., 2017; Feng et al., 2016). Moreover, these approaches are time consuming and labor intensive. Considering these disadvantages, research in the field of continuous drug nanoparticle preparation is an area to be considered. The existing challenges in drug delivery and their solution through microfluidics is shown in the Fig. 5.

The emergence of microreactor technology offers a new method for producing drug nanoparticles. Within the microfluidics system, it is possible to achieve conditions that are not accessible in batch approaches. The ability of microreactor to rapidly mix the reagents by providing high surface area to volume ratio has made it an attractive technology for encapsulating drug particles (Demello, 2006). Here, the characteristic time for mixing can be tuned to be faster than the timescale for nanoparticle precursors to nucleate and grow. Therefore, in microfluidics nucleation and growth process can be isolated as a function of channel length and particle agglomeration can be avoided (Tai et al., 2016). Furthermore, free convection environment in this technology produces high quality drug crystals (Sauter et al., 2007).

The major challenge in encapsulating drug within polymeric nanoparticles is the inability to control the mixing process required for nanoparticles preparation. The rapid and tunable mixing through microfluidics has proven to overcome this challenge in recent years. Martin et al. compared convention and microfluidic approach to prepare efavirenz loaded PLGA nanoparticles. In comparison with conventional method microfluidics approach showed high drug loading (10.8% versus 3.2%), greater drug association efficiency (80.7% versus 32.7%), and smaller particle size (83 nm versus 133 nm) (Martins et al., 2019). Bramosanti et al. also demonstrated the efficiency of microfluidics method to control the size, polydispersity of nanoparticles, and especially the amount of drug entrapped compared to traditional bulk methods. The drug loading efficiency of 74% was observed for microfluidics as compared to 10% bulk method (Bramosanti et al., 2017).

Kamat et al. compared conventional and active microreactor for synthesis of chitosan nanoparticles by ionic gelation. The single reaction chamber setup for conventional and microreactor were modeled and analyzed through Comsol Mutiphysics 4.4. As shown in Fig. 6(a, b) the concentration profile obtained for microreactor showed uniform mixing of the liquid in comparison with unmixed gradient observed in the conventional model at same time interval. Simulated data showed much higher mixing efficiency for microreactor compared to conventional technique, with a maximum of ~90% in 30 s (Fig. 6(c, d)). The validation of model was done experimentally. It can be observed from Fig. 6(e, f) that mixing efficiency for microreactor was much higher than conventional approach for experimental results also. The maximum mixing efficiency obtained experimentally for microreactor was about 80% which was in good agreement with the simulated results (~90%) (Kamat et al., 2015).

Bao et al. investigated two approaches, microfluidics and dialysis method for preparation of docetaxel-loaded-PLGA-PEG-Mal-based micelles. Smaller average particle size of 72 ± 1 nm with 0.072 PDI was obtained for micelles prepared by microfluidics method (DMM). Whereas, for micelles prepared using dialysis method (DMD) the particle size was in range of 102–144 nm with 0.390 PDI. Furthermore, targeting docetaxel-loaded micelles (TDMM) were prepared by attaching cyclic RGDfK (arginine-glycine-aspartic acid-phenylalanine-lysine) to the surface of DMM. More importantly, higher drug loading was observed for microfluidic method. Fig. 7 shows the physicochemical characterization obtained for docetaxel-loaded micelles (Bao et al., 2018).

Table 5 – Literature findings on microfluidics for drug encapsulation and nanonization.

API/drug	Agent	Micromixer	Combination technique	Motive	Results						Remark/s	Reference
					EE	DR	PS	Morphology	PDI	ZP		
Ketoprofen	PMMA, Cremophor ELP (stabilizer)	T-type, HPIMM, and K–M type	Nanoprecipitation, Spray drying	To control the NPs size and to investigate and compare the effect of spray drying on NPs EE and DR	Around 45	Up to 70 in 6 h	100–210	–	~0.2	–	EE for NPs obtained from spray drying was slightly less than that of non-spray dried NPs K–M type micromixer showed best results	Ding et al. (2019)
Curcumin	Sodium cholate, Tween 80, PLGA (RG 752H, RG 502H, RG 504H), PVA, PEG 2000, PEG 5000	Staggered herringbone	Antisolvent precipitation	Sustained release	Around 50	Sustained release for 7 days	Below 200	Spherical	0.15	–	Cytotoxicity assay determination PEG 2000 incorporated PLGA NPs gave better result	Morikawa et al. (2018)
Cinnarizine	Niosomes, Span 60, Cholesterol, Cremophor ELP, Cremophor RH40, and Solutol HS15	Cartridge	Antisolvent precipitation	To compare microfluidics and thin film hydration for NP synthesis.	0.37–8.9	50 in 24 h	172–355.3	Circular	0.011–0.209	−4.486 to −0.764	Niosomes with amorphous nature were obtained using microfluidic method.	Yeo et al. (2018)
Efavirenz	PLGA and Tween 80	–	Precipitation	To develop a DDS able to carry drug to the brain administered by intravenous route.	–	50 within 24 h	72.8	Round	0.086	-14.1 ± 1.3	High association efficiency and drug loading was observed compared to conventional method 1.3-fold higher permeability than free drug	Martins et al. (2019)

Table 5 (*Continued*)

API/drug	Agent	Micromixer	Combination technique	Motive	Results						Remark/s	Reference
					EE	DR	PS	Morphology	PDI	ZP		
Dexibuprofen	Poloxamer 407, PVP K-30, HPMC	Y-type with inlet angle 10°	Antisolvent precipitation	Solubility and bioavailability enhancement	–	85.4 in 5 min	45	Crystalline with homogenous distribution	0.19	−22.1	60 days stability of NPs at 4 °C and 25 °C 96.9	Khan et al. (2018)
Itraconazole (ITZ)	Poly(vinylpyrrolidone-vinyl-acetate) (PVPVA), Poloxamer 407, Poloxamer 188	T-type	Nanoprecipitation and ultrasonic spray drying (USD)	To demonstrate the feasibility of MD-USD for continuous NPs preparation	–	–	100–300	Spherical	–	–	NPs size was significantly reduced in case of USD compared to microreactor PVPVA showed amorphous NPs with relatively narrow size distribution	Zhang et al. (2018)
Bndesonide	–	T-type and acoustically enhanced (Ultrasound probe)	Antisolvent precipitation	Uniform NPs without addition of stabilizer	–	–	Less than 150	–	0.044	–	Despite lack of stabilizer particle size distribution remained constant and no coalescence 40-fold reduction in size	Le et al. (2018)
Ribavirin	PLGA	Hydrodynamic flow focusing	Antisolvent precipitation	Drug encapsulation for chemothera-pic treatment	–	Sustained release	58	Spherical	0.114	–	Comparison with bulk precipitation Loading efficiency 74% as compared to 10% for bulk method	Bramosanti et al. (2017)
Curcumin	PVA	Flow focusing	Antisolvent precipitation	To develop and optimize drug loaded NPs	–	–	63.12	Spherical pearl like	0.02–0.3	Between -20 to -60	Optimized value of NPs was obtained at high and low Re not at intermediate Re	(Rahimi et al., 2017)

Table 5 (*Continued*)

API/drug	Agent	Micromixer	Combination technique	Motive	Results						Remark/s	Reference
					EE	DR	PS	Morphology	PDI	ZP		
Paclitaxel (PTX), Sulforaphane (SFN)	Hypermellose acetate succinate (HF)	Multiplexed design	Antisolvent precipitation	Controlled release	–	Complete DR for both APIs at pH 7.4	60–450 for PTX and 70-550 for SFN	Spherical for both APIs	Less than 0.2	–	Production capacity of 700 g/day at 1300 Re was achieved High batch to batch reproducibility was observed	Liu et al. (2017)
Paclitaxel	Polymethylmethacrylate (PMMA), Eudragit S100, Pluronic F68	T-type	Nanoprecipitation	To identify parameters governing the size and distribution of NPs in microreactor	71.73–86.67	Sustained release up to 96 h	105.32–139.42	Spherical and uniform	0.173–0.21	–	Comparison with batch process Used commercially available AmAR1 microreactor	Dobhal et al. (2017)
Cyclosporin	PLGA	T-type, Y-type, and Cross micromixer	Emulsification	To validate the efficiency of microfluidics to produce drug loaded monodisperse NPs	91.5	–	211	Spherical	Reduced	–	Best result obtained for cross micromixer Mechanically durable, easy to operate, and has high production capacity of 10 g/h	de Solorzano et al. (2016)
Amphotericin-B (AmB)	Chitosan	Circular 3 chambers active (magnetic actuator) micromixer	–	To carry out modeling and synthesis of NPs in conventional and active microreactor	82.7 for 3 chamber and 59.7 for 2 chambers	52 in 120 h and 80 in 336 h	130	Spherical	–	39.8	Magnetic actuator length 0.5 mm NPs were effective against Candida and had a good hemocompatibility	Kamat et al. (2015)

Table 5 (*Continued*)

API/drug	Agent	Micromixer	Combination technique	Motive	Results						Remark/s	Reference
					EE	DR	PS	Morphology	PDI	ZP		
Losartan potassium (LP)	Ethyl cellulose (EC), Tween 80	Y-type	Antisolvent precipitation	Sustained release	82.8	23.95 in 1 h followed by sustained release for 19 h	357.8	Spherical	0.469	–	Increased bioavailability and sustained release as compared to marketed formulation	Patil et al. (2015)
CRS 74	Chitosan, Poloxamer 407, HPMC, Sodium dodecyl sulphate (SDS), Tween 20	T-type	Liquid anti solvent crystallization	To improve dissolution rate using various additives	–	42.43 in 30 min	596–918	–	–	16.3	Best result for Poloxamer-407 with concentration > CMC in organic phase and chitosan in aqueous phase	de Paiva Lacerda et al. (2015)
Sorafenib (SFN), Celecoxib (CEL)	Acetylated dextran (Ac-Dex), Hypermellose acetate succinate (HPMC-AS), PLGA	Flow focusing	Emulsification	To prepare monodisperse hollow microparticles and simultaneously encapsulate drug	96–97 for both drugs with Ac-Dex	pH sensitive for both drugs	2700–6800	Spherical	–	–	–	Vasiliauskas et al. (2015)
Dexamethasone (DEX)	PLGA	Hydrodynamic flow focusing	Antisolvent precipitation	Reproducible production of stabilized polymeric NPs	93	100 in 60 min	34	Spherical	–	–	Comparison with bulk nanoprecipitation technique Increased drug loading from 0.1 to 0.9 mg DEX/mg	Chronopoulou et al. (2014)
Rifampicin	Tween 20	Flow focusing	Antisolvent precipitation	To reduce particle size and enhance dissolution rate	–	80 in 45 min	100–1120	Spherical	–	–	Particles showed amorphous profile	Schianti et al. (2013)

EE: encapsulation efficiency (%), DR: drug release (%), PS: particle size (nm), PDI: polydispersity index, ZP: zeta potential (mV), HPIMM: high pressure interdigital multilamination micromixer.

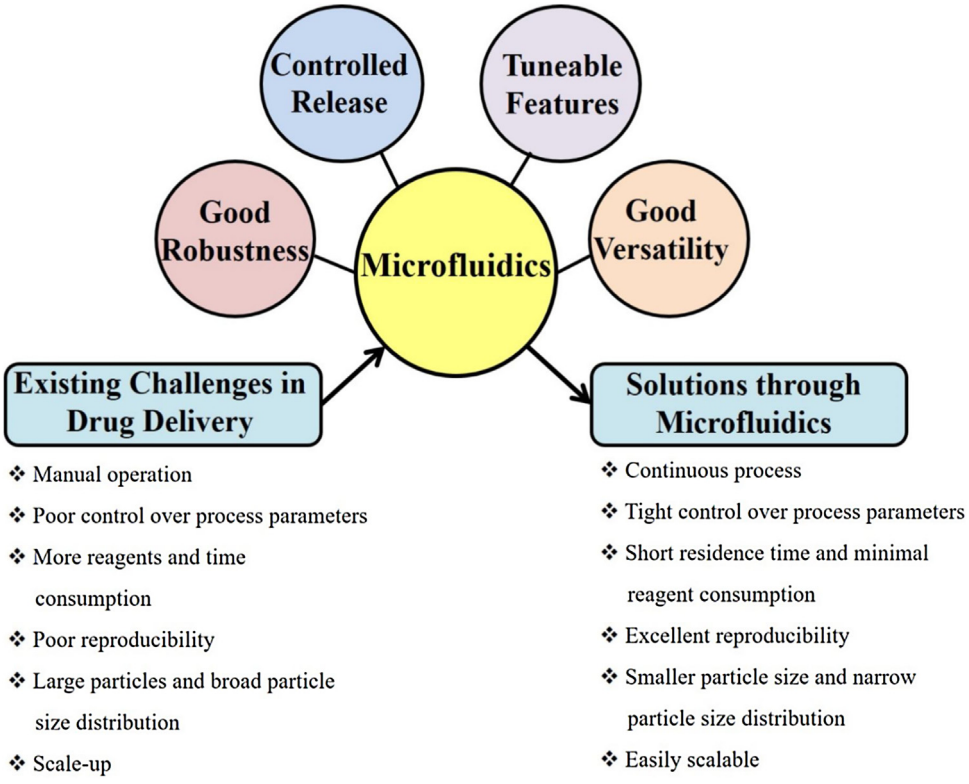

Fig. 5 – Existing challenges in drug delivery and their solution through microfluidics.

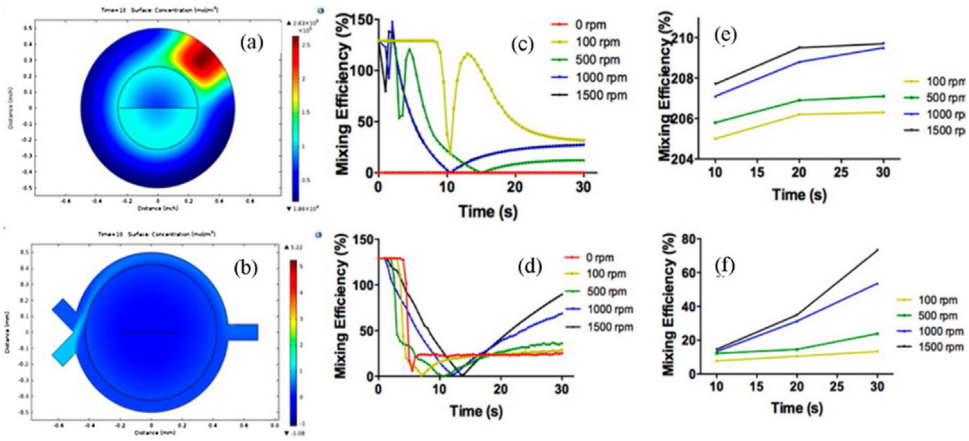

Fig. 6 – Concentration profile of mixed liquid for conventional and microreactor (a, b); mixing efficiency calculated from simulation using Comsol Multiphysics 4.4 for conventional and microreactor (c, d); mixing efficiency evaluated from experiments for conventional and microreactor (e, f). Adapted from Kamat et al. (2015) with permission of American Chemical Society.

Shrimal et al. prepared poloxamer 407 encapsulated telmisartan (TEL) nanoparticles through microreactor to enhance the solubility and bioavailability of TEL. The effect of mean residence time on particle size distribution of TEL nanoparticles in microreactor was also investigated by varying the solvent flowrate. It was observed that at higher residence time (low flowrate) broad particle size distribution was observed. Moreover, it was reported that decreasing the residence time in microreactor resulted in smaller particle size and narrow particle size distribution (Shrimal et al., 2019). Literature findings on microfluidics for drug encapsulation and nanonization are reported in Table 5.

In the past few years, microstructured reactor for liquid–liquid phase reaction to produce drug nanoparticles has been widely investigated. Based on the reacting phase involved, microreactor system can be divided into two categories; continuous flow (single phase) microfluidic system and droplet flow (multiphase) microfluidic system (Krishna et al., 2013; Zhao et al., 2011).

3.1.1. *Continuous flow microfluidic system*

In the production of drug nanoparticles, single phase systems are most widely studied due to their simplicity, and ease of controlling process parameters. Here, two or more miscible solvents are mixed in a continuous flow reactor for

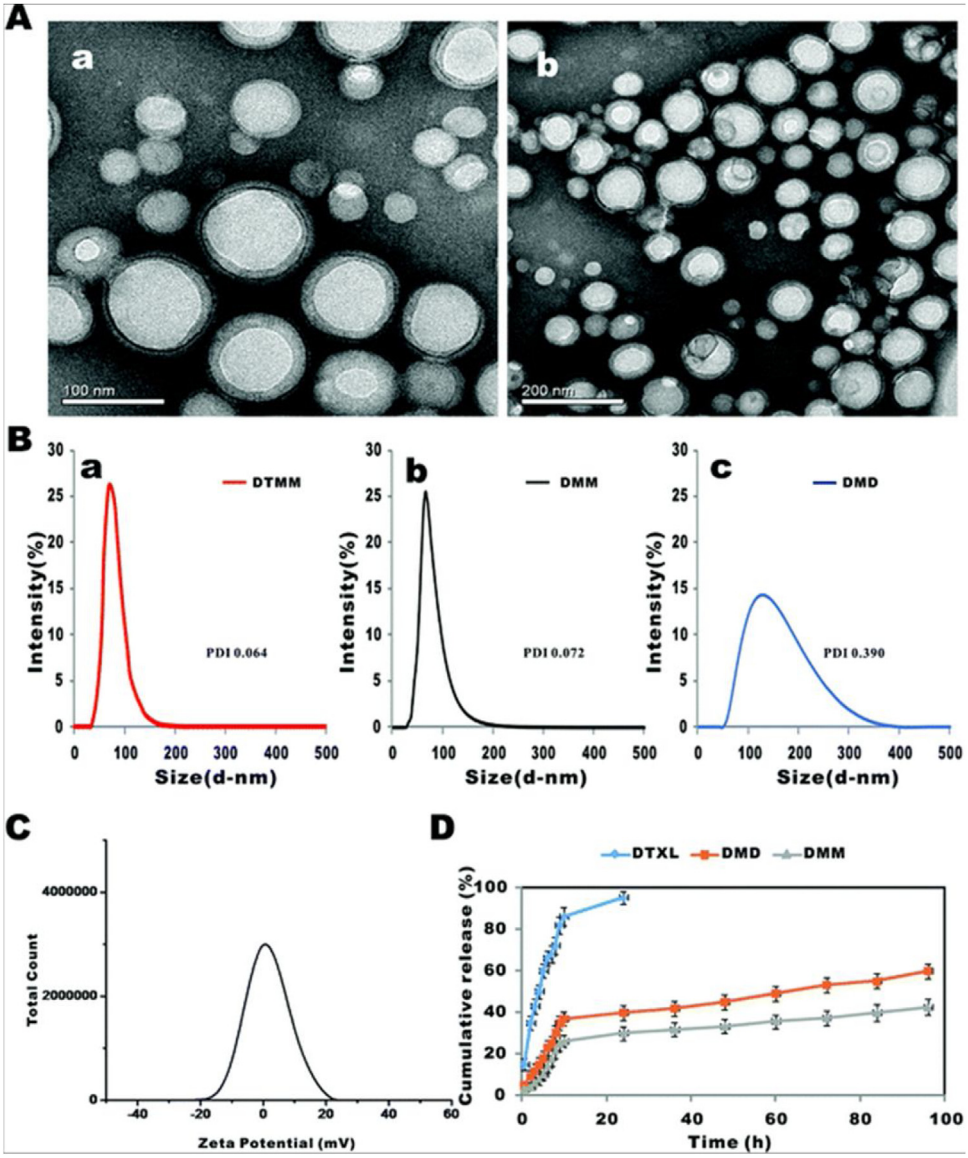

Fig. 7 – Physicochemical characterization of docetaxel-loaded micelles (A) TEM images of drug-loaded micelles prepared by microfluidics (a) Scale bar-100 nm (b) Scale bar-200 nm. (B) DLS analysis for size distribution and polydispersities of different micelles (a) DTMM, (b) DMM, (c) DMD. (C) Zeta potential of micelles (D) Release curve obtained by dialysis in PBS release medium. Reproduced from Bao et al. (2018) licensed under Creative Commons Attribution-NonCommercial 3.0 Unported License (CC BY-NC 3.0).

drug nanoparticle preparation. For most of the reaction, the Reynolds number lies in the laminar flow region owing to diffusion controlled mixing. To enhance mixing, turbulence in the microchannel is triggered by bending and stretching the channels (Stroock et al., 2002). Karnik et al. studied drug encapsulation in hydrodynamic flow focusing microfluidic reactor by using two miscible solvents, acetonitrile and water. By rapid and tunable mixing, tight control over precipitation of PLGA-PEG copolymer was achieved. Homogenous and smaller particles were produced in microreactor when compared with bulk nanoprecipitation technique (Karnik et al., 2008). Patil et al. also investigated nanoprecipitation technique to prepare losartan loaded nanoparticles in continuous flow tubular microreactor. A sustained release formulation was prepared for oral therapy of hypertension. Microreactor precipitation method was suggested as a promising approach for achieving higher encapsulation efficiency and sustained drug release (Patil et al., 2015). Results shown by Capretto et al. demonstrated that continuous flow microfluidic reactor provides an excellent platform for drug nanoprecipitation with enhanced controllability, reproducibility, and homogeneity of the size characteristics (Capretto et al., 2011). The factors that affect the nanoprecipitation process in microfluidics are reaction time, temperature, concentration of solvent, flow rate ratio of solvent to antisolvent, and mixing patterns. The homogenous environment in a continuous flow reactor yields smaller nanoparticles with a narrow particle size distribution (Liu et al., 2015). Moreover, high throughput production with great reproducibility of drug nanoparticles is highly desirable in pharmaceutical industries.

3.1.2. *Droplet flow microfluidic system*

In contrast with continuous flow systems, droplet flow or segmented flow systems involve two or more immiscible fluids (Günther and Jensen, 2006). Droplet based microfluidics is used to produce emulsion, microdroplets, and microparticles. Droplets are generated due to the shear force generated at two immiscible fluids interface. The continuous or aqueous

phase creates viscous stress on the immiscible organic or dispersed phase, which is balanced through surface tension. The viscous shear stress tries to elongate the interface, while the competing surface tension tries to decrease the interface area (Yu et al., 2010). Droplets are generated above critical stress and are characterized through the capillary number (ratio of viscous force to surface tension). The parameters that play an important role in droplet microfluidics are flow rate, viscosity, and surfactant. Mixing in segmented flow system also depends on the selection of suitable immiscible phase and the channel geometry (i Solvas, 2011).

The droplet microfluidics offers the advantages of quick heat and mass transfer due to adequate mixing efficiency. In comparison with the conventional approaches, droplet based microfluidic system produces drug particles with narrow size distribution (Wang et al., 2008). de Solorzano et al. investigated emulsification process in the interdigital microfluidic reactor to produce cyclosporine loaded PLGA nanoparticles. Mechanically durable and easy to operate microreactor had a high production capacity of 10 g/h. Reaction conditions showed zero reactant adsorption on microchannel surface and no agglomeration, thus rendering droplet microfluidic systems suitable for drug encapsulation (de Solorzano et al., 2016). Unlike, in single phase microfluidics, multiphase microfluidic systems allow to individually control each droplet, hence generating a microfluidic device that can be transported, mixed, and analyzed (Fair, 2007). It also provides advantages of high reproducibility, greater production capacity, and less residence time. Despite the high aspect ratio of single phase microfluidics, clogging and fouling remains the major challenges. Whereas, in droplet flow, microfluidics system drug is encapsulated inside liquid droplet which reduces the channel blockage risk. However, most of the carriers prepared using droplet microfluidics are in the micron range due to the size limit of the droplet. Furthermore, microfluidic emulsification using polymer dispersed precursors is challenging due to extremely low interface tension. Some external field (e.g. mechanical vibration, ultrasound, and electric field) is required to drive the droplet generation (Song et al., 2013). Recently, Rezvantalab and Moraveji reviewed the synthesis of PLGA NPs in microfluidics for drug delivery. Based on literature survey, the relationship between the type of microfluidics and the final particle size of PLGA-based drug delivery systems was presented. It was observed that for continuous microfluidics the particle size varied in 10−1000 nm range. Whereas, for droplet based microfluidics the particle size was between 10^3–10^6 nm. It was concluded that the organic phase solvent and microfluidics configuration controls the particle formation step, pace, and consequently the particle size (Rezvantalab and Moraveji, 2019).

3.2. *Scale-up of microreactor*

Considering the ever growing potential of NPs in industrial applications and to realize the translation of microfluidic device in the pharmaceutical applications, it is important to scale up this technology for mass production. The key advantage of microreactor technology is its miniaturized fluidic environment. To scale up microreactor while retaining its substantial advantages is in fact a major challenge. Scale-up strategies include (a) Parallel numbering up (b) Series numbering up and (c) Scale out (Zhang et al., 2017). One of the most promising approaches to scale up microfluidics is parallelization of the microreactor. In this approach, multiple channels or reactors are placed in parallel so that daily production rate can directly multiply with the same properties as those prepared at bench scale. Through this approach, hydrodynamics and heat/mass transfer characteristics are retained, but it requires complex fluid flow distribution and control. In addition, such an arrangement requires a separate set of pumps or pressure controlling system for the fluid inlet. Thus, integration among these parallel devices is required to minimize the number of pumps and other equipment. In a recent study, nanoparticles production capacity of 3 kg per day was achieved in a versatile coaxial turbulent jet mixer which is suitable for pharmaceutical industrial scale production (Liu et al., 2015). The series numbering up approach utilize multiple microreactors in series, keeping one precursor at a high flow rate and adding another stepwise in series. Such an approach has advantages of circumventing the need for fluid distributors, easy flow control, and lower cost. However, the possibility to scale up this approach is limited, due to the inability to increase flow rates unlimitedly. The last approach of scale out involves selective dimension enlargement. The microchannel size can be increased suitably to obtain the desired throughput. The enlargement of the flow path is only acceptable if the mixing, mass, and heat transfer performance are maintained (Kirschneck and Tekautz, 2007). Wang et al. investigated a pilot scale reactor utilizing the combination of scale out and numbering up as a more maneuverable and economic approach. To assist in the analysis and optimization of fluid distribution, CFD was employed. Ten parallel units were integrated to form an enhanced capacity microreactor which showed reduced pressure drop, excellent product selectivity, and stable operating performance. The increment of 160 times in throughput and product selectivity of 96% was achieved in the pilot plant which was only 1–2% lower than lab scale microreactor (Wang et al., 2014).

3.3. *Beyond microfluidics*

The combination of microfluidics and ultrasound for drug encapsulation is a new and emerging field. Such a combination is technically feasible and often leads to synergistic results. In droplet microfluidic systems, the preparation of stable emulsion is difficult due to extremely low interfacial tension while using polymer precursors. The poor solubility of the organic phase in the aqueous phase makes the rate of reaction slow and requires vigorous mixing to ensure maximum contact between two immiscible fluids. Moreover, it is difficult to produce particles with size less than 1 μm in droplet microfluidics, hence, a combination of a microreactor with ultrasound for intensification of mass transfer might open a new door for drug encapsulation. While applying ultrasound in liquid medium, micron size cavitation bubbles are generated in a microchannel. For immiscible liquid–liquid system, the collapse of the cavitation bubble at the liquid–liquid interface will disrupt the interface and will eventually enhance mixing to obtain very fine emulsion (Wang and Rajendran, 2007). Iida et al. (2004) have confirmed the cavitation phenomenon in microchannel through video imaging. Basiri et al. investigated transesterification reaction in ultrasound assisted microreactor. Results revealed that the intensification process minimized the reaction time, temperature, alcohol-to-oil molar ratio as well as energy consumption (Basiri et al., 2016). Jolhe et al. studied ultrasound assisted preparation of performic acid in continuous microstructured reactor (Jolhe et al., 2017). In addition, due to small channel dimension, sus-

ceptibility of clogging is a nightmare for microreactor. The implementation of ultrasound will apply an external force perpendicular to the flow direction, which could in turn produce a transverse flow and enhance mixing directly. Horie et al. have reported that the combination of ultrasound with microreactor prevents clogging in the microchannel (Horie et al., 2010). But, very few literatures report the combination of these technologies. More research and development on this intensified technology could make a clinical translation of nanomedicines possible.

4. Conclusions

Over the years, various techniques have been widely studied to prepare drug nanoparticles. In this review, we have presented probably the most generally studied methodologies along with a recently emerging technology mocrofluidics. From couple of years, spray drying, high pressure homogenization, and ultrasound have been explored by numerous researchers to encapsulate drug in micro/nano particles for achieving desired therapeutic effectiveness. Using the mentioned techniques, there are still some challenges which are hurdles in clinical translation of nanomedicines.

The emergence of microfluidics has overcome the limitations of these techniques and has proved itself as a simple, and powerful tool for encapsulating drug into polymeric particles with high encapsulation efficiency, narrow particle size and particle size distribution, and good reproduciblity. On the basis of reacting phases involved, for liquid–liquid systems microreactor are classified as continuous flow and droplet flow microfluidic systems. The continuous flow microfluidic systems provides excellent platform for drug nanoprecipitation with enhanced controllability, reproducibility, homogeneity of the size characteristics, and smaller nanoparticles with narrow particle size distribution. On the other hand, droplet flow microfluidics offer advantages of quick heat and mass transfer, high reproducibility, greater production capacity, and less residence time. However, droplet flow microfluidic emulsification using polymer dispersed precursors is quite challenging. Moreover, droplet microfluidics produces particles in micron range due to size limit of the droplet. In order to overcome these issues related to droplet microfluidics we proposed to combine microfluidics with ultrasonication. To the best of our knowledge, no detailed study has been reported on combination of microfluidics with ultrasound to encapsulate drug nanoparticles through emulsification. Hence, this review opens few more possibilities to explore which can change the future of pharmaceutical industries.

Declaration of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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