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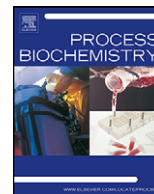
Review

Single enantiomeric β-blockers—The existing technologies

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A B S T R A C T

A number of β-blocking drugs are available in the world market, only few compounds are found as single enantiomers. The need to use the single enantiomeric β-blockers affects development of drugs and technology. Many processes have been exploited to replace the existing racemates. Two main routes are established: (1) asymmetric syntheses and (2) racemic resolutions. The syntheses give medium-high yields and excellent enantiomeric excess, but the resolutions are limited by 50% yield. Both technologies involve new techniques such as dynamic kinetic resolution (DKR) and membrane-based extraction. The synthetic ways utilise various substrates and catalysts. A simultaneous formation is also afforded by these processes. They offer oriented alternatives to the single enantiomeric β-blockers. Resolutions of the racemates appear with many attractive separation methods. Direct or indirect resolutions show excellent characteristics and produce high enantiomeric excess. The existing processes operate continuously at mild operating temperatures compared to the asymmetric synthesis. *In situ* separation is also exploited. Development of the single enantiomeric β-blockers using the DKR based on enzymatic membrane(s) is encouraged. Integration of acetylation, racemisation and hydrolysis followed by separation of the enantiomers in the enzymatic membrane reactors could be a better option in resolution and separation of the β-blocker racemates.

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1. Introduction: status of β-blockers

The need to use single enantiomers in medication forces authorities to tighten regulations on drugs. The United States Food and Drug Administration requires enantiomeric studies and justification for approval of racemic drugs [1,2]. The evaluations lead to the development of drugs and technology [3]. Since then a lot of efforts have been exploited to form the single enantiomers [4]. However, until 2002 the number of single enantiomeric drugs approved to be sold in the world markets was 39% [5]. In general, the cardiovascular drugs were the highest portion of the sold single enantiomers [6].

Beta adrenergic receptor blocking agents or popularly known as β-blockers are a group of drugs consumed in cardiovascular therapies. The drugs treat high blood pressure, heart failure and myocardial ischemia diseases [7,8]. They have similar functions to calcium channel- and angiotensin-II-blockers, but are found mostly as racemates as shown in Table 1 [8–28]. Many β-blockers are available in the United States and European markets [29,30] since the first launch in 1960s [31], however only few drugs are sold as single enantiomers. Hence, major clinical and research purposes are based on the racemates.

The β-blocker enantiomers should be used individually [32]. The enantiomers often have different pharmacokinetic and pharmacodynamic properties [33,34]. Although Sheldon [35] concluded the distomers (less active enantiomers) show no serious side effects, they essentially do not give the β-blocking effects or reduce the overall drug selectivity [36], produce the same side effects as the eutomers (more active enantiomers) [37] or the distomers are possible to cause the adverse effects [38,39] such as the contraceptive activity [40,41]. Most β-blockers depend on (S)-enantiomers for the disease therapies [42,43]. In general, the (S)-enantiomers are more potent than the distomers [44] in 10–500-folds [13,45–61].

Some methods were developed for synthesis of the single enantiomeric β-blockers, but separation of their racemates was not carried-out easily [42]. Biocatalytic approaches of the single enantiomers or precursors had been reported [62]. Various substrates processed by hydrolases were revealed by this report. Liquid chromatography, capillary electrophoresis, super- and sub-critical fluid chromatography and capillary electrochromatography were used in separation of the adrenergic drugs in clinical and pharmaceutical analysis [63].

This article is aimed to review the processes employed to prepare the single enantiomeric β-blockers. It covers efforts to replace the existing racemic β-blockers from the asymmetric synthetic perspectives. Progress on resolution of the existing racemates is considered important to be summarised. The article also describes other processes, which are newly developed. Resolution of the β-blockers using enzymatic membranes is highlighted.

2. Single enantiomeric-based processes

2.1. Routes to single enantiomers

Commonly two ways are developed to harvest the single enantiomers. The first is recovery of natural compounds, which provides massive single enantiomers. However, although artificial syntheses produce single enantiomers, many synthetic products such as drugs are available as racemates [64,65]. To replace these racemates, directs syntheses of the single enantiomers and/or resolutions of the racemic compounds are developed [66] through chemical or chemo-enzymatic pathways [67]. A general route to the single enantiomeric β-blockers is presented in Fig. 1. The syntheses use either racemic or chiral compounds as raw materials, whilst the resolution processes consume the racemates or racemic esters or diastereomeric derivates. The crystallisation processes are not popular. Other methods such as whole-cells reduction, dynamic kinetic resolution and enantioselective extraction have also been integrated.

2.2. The existing single enantiomeric β-blockers: highlight of processes

Various technologies were employed to give the existing single enantiomers [12,68–109]. (S)-bunolol was prepared from an oxiranic intermediate without formation or resolution of its racemate [110]. Previously the racemic bunolol synthesized from hydroxytetralone and epichlorohydrin was resolved hydrolytically using (−)-tartaric acid [109]. (S)-penbutolol was made by methods of regioselective alkylation of phenol-cyclopentanol, resolution of its racemate, enzymatic hydrolysis of its acetate derivative or epoxidation of the allylic alcohol [111–114]. Resolution of the racemates were also conducted by changing the racemic mixtures into pairs of diastereomeric urea then separated and purified [115,116].

3. The asymmetric syntheses: synthetic ways to replace the existing racemic β-blockers

The technology converts a prochiral substrate enantioselectively by its reaction with a chiral addendum in which the asymmetry is introduced into the molecule [117]. It uses chemical catalysts and biocatalysts. The chiral molecule is developed from the prochiral substrate chemically, but resolution of the chiral molecule is carried-out by a chemo- or biocatalyst. It is the only way to make the single enantiomeric drugs chemically. Five processes are found based on the asymmetric formation and racemic resolution. A broad range of substrates are exploited to form the single enantiomers through multi-step batch processes.

3.1. Chemo-catalysis
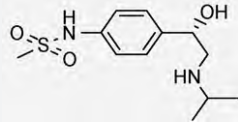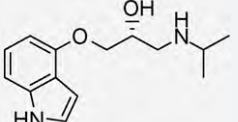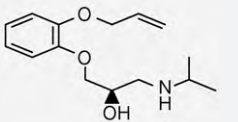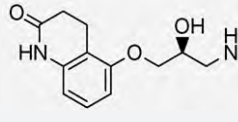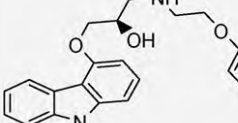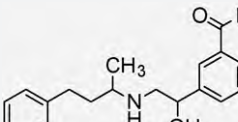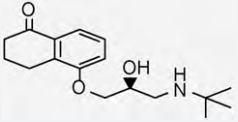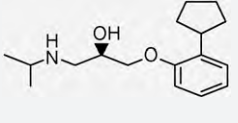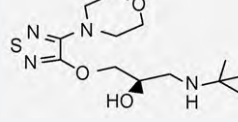
Many chemical catalysts have been employed by chemo-catalysis to transform a prochiral substrate to an enantioenriched product. The asymmetry is introduced into one of the reactions by a chiral synthetic catalyst/addendum [118]. If the chiral addendum is used, the asymmetric reaction requires a non-chiral catalyst to promote the reaction. The technology gives great advantages such as providing efficient reaction, short reaction time and mild reaction conditions [119]. Two catalysts that introduce the asymmetric molecules are found: (a) Metal-ligand complex catalysts and (b) Organocatalysts. The performances [79,120–137] are given in Table 2.

During the metal-ligand catalysis process, the stereoselection was achieved by connecting an enantiomeric ligand to a transition metal and allowing the resulting complex to act as a template or scaffold to which the substrate molecules bind [133]. The (optically) inactive substrates were converted by the complex molecule to optically active intermediates through the ring open-

Table 1
Market status of β-blocker compounds.

Market status	Category	Generic name	Active isomer	Chemical structure	Brand name (*maker*)
Racemic compounds	β1-selective	Acetobutolol (ACE)	S		Sectral (*Rhone*) Monitan (*Wyeth*)
		Atenolol (ATE)	S		Tenormin (*Stuart*) Tenordate (*Astra*)
		Betaxolol (BET)	S		Kerlone (*Lorex*) Optipres-S (*Cila*)
		Bisoprolol (BIS)	S		Zebeta (*Unisearch*) Cardicor (*Merck*)
		Esmolol (ESM)	S		Brevivloc (*Reckitt*) Esmolol (*Bedford*)
		Metoprolol (MET)	S		Lopressor (*Novartis*) Toprol (*Astra*)
		Nebivolol (NEB)	SRRR		Nebilet (*Menarini*) Nebicip (*Cila*)
	Non-selective	Alprenolol (ALP)	S		Aptol (*Globopharm*) Betacard (*Beecham*)
		Carazolol (CAR)	S		Conducton (*Klinge*) Suacron (*Bayer*)
		Nadolol (NAD)	S		Corgard (*Sanofi W*) Corzide (*King*)
		Propranolol (PRO)	S		Inderal (*Wyeth*) Inderal LA (*Zeneca*)

Table 1 (*Continued*)

Market status	Category	Generic name	Active isomer	Chemical structure	Brand name (*maker*)
Single enantiomers		Metipranolol (MEP)	ND	ND	Optipranolol (*Bausch*) Trimepranol (*Slovak*)
		Sotalol (SOT)	S		Betapace (*Berlex*) Sorine (*Upsher*)
		Pindolol (PIN)	S		Visken (*Sandoz*) Barbloc (*Alpha*)
		Oxprenolol (OXP)	S		Trasicor (*Ciba*) Trasitensin (*Novartis*)
		Carteolol (CRT)	S		Cartrol (*Abbot*) Carteol (*Bausch*)
	Mixed α1/β-blocker	Carvedilol (CRV)	S		Coreg (*Glaxo*) Eucardic (*Roche*)
		Labetalol (LAB)	RR		Normodyne (*Schering*) Trandate (*Evans*)
	β1-selective	Betaxolol	S	Previous picture	Betaxon (*Alcon*)
		Atenolol	S	Previous picture	Nutin, Nutin SA, Nutin-7, Atpure (*Emcure*)
		Metoprolol	S	Previous picture	Metpure XL, Metpure AM (*Emcure*)
	Non-selective	Bunolol (BUN)	S		Apo-Levobunolol (*Apotex*) AKBeta (*Akorn*)
		Penbutolol (PEN)	S		Levatol (*Schwarz*) Betapressin (*Aventis*)
		Timolol (TIM)	S		Timoptic (*Merck*) Betimol (*Santen*)

Fig. 1. Pathways to the single enantiomeric β-blockers.

ing reaction, asymmetric hydrogenation, asymmetric epoxidations, regioselective substitution, asymmetric dihydroxylation, metal-catalysed kinetic resolution, hydrolytic kinetic resolution, ring opening kinetic resolution or catalytic asymmetric nitroaldol reaction. Various transition metals and synthetic ligands were exploited giving excellent yields and enantiomeric excess (ee). The reactions were constructed by incorporating reagents/other catalysts operating at different conditions. Many alcohol-based substrates a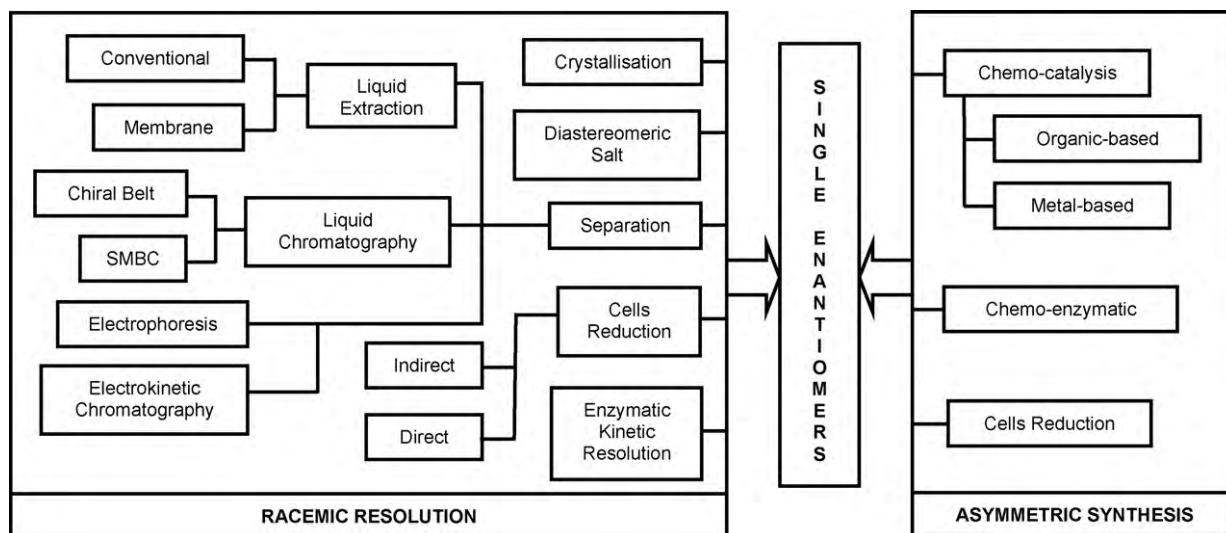s naphthol, phenol and sorbitol [120–122,128,130,132,138] were used. Others exploited racemates as the starting materials [139].

Concise and efficient enantioselective routes were established [128,129]. For example, the aromatic-based compounds required 2–8 reaction steps to produce the single enantiomers. The (S)-(−)-propranolol was collected after 4 steps through asymmetric hydrogenation of α-naphthol using (2S,4S)-MCCPM-Rh(I) catalyst [121,122]. However, the metal-ligand complex catalysis was associated with extremely low operating temperatures.

The temperatures below 0 °C were employed for several reactions in the metal-ligand-based catalysis. The Sharpless asymmetric epoxidation was conducted at −20 °C [128]. The temperature of −25 ± 5 °C had also been used [123]. The ozonolytic cleavage-reduction was performed at −78 °C [129].

Long reaction steps were needed to produce compounds with many chiral centres. A recent experiment conducted to form the (S,R,R,R)-nebivolol from a racemic substrate required two reaction parts: parts to produce left (S,R) and right (R,R) fragment [127]. Each fragment demanded at least 7 steps before they were combined to form the (S,R,R,R)-nebivolol. Candrasekhar et al. [128] developed the 9 reaction steps to form fragments of the same drug.

The second type of the chemo-catalysis employs a purely organic, small molecular weight and metal-free compound to catalyse a chemical reaction [140,141]. The organocatalysis has achieved highly enantioselective and efficient synthesis of the β-blockers by employing the organo-catalysed asymmetric reaction as a key step and the source of chirality [134]. Performance of the technology is shown in Table 2. It is an attractive solution for preparation of compounds that do not tolerate metal contamination [142]. The process was operated at relatively mild temperature condition, however, the temperature as low as −20 °C had been used to complete the asymmetric α-aminoxylation reaction.

The chiral organocatalysts form chiral intermediates from the prochiral substrates. For example, reduction of carbonyl group of 4-(chloroacetyl)-methanesulfonanilide catalysed by the (S)-2-CBS-methyl-oxazaborolidine gave the chiral chloro alcohol [135].

However, reactions based on the chiral building blocks had also been developed.

Short reaction steps were performed. Development of the (R)-nifenalol required only 2 reaction steps [119]. Firstly, the substrate, α-sulfonyloxy ketone, was reduced to an (R)-diol in the presence of the chiral catalyst and N-ethyl-N-isopropylaniline-borane in tetrahydrofuran at 25 °C. Then the (R)-1,2-diolmonotosylate was aminated at room temperature by isopropylamine or 3,4-dimethoxyphenylethylamine to give the (R)-nifenalol.

3.2. Chemo-enzymatic kinetic resolution catalysis

The process combines chemical catalysed reactions and enzymatic kinetic resolution. The substrates are converted by many reactions, but the formed racemates are resolved by the enzymatic process instead of the chemical catalysis. It develops racemic intermediates in the reactions, but the process can use racemates as starting materials. Formation of single enantiomeric intermediates by the enzymatic process is the key of this technology [143]. Performance of the technology is presented in Table 3 [38,40,41,143–147].

The chemical part plays a major role. It produces high yields at mild operating conditions. Though the enzymatic resolution is the technology key, this part provides the optically active intermediates. For example, Kapoor et al. [145] used 4-nitrophenacyl-bromide (2), a non-optical molecule produced from the substrate halogenation (4-nitroacetophenone (1)), to generate a racemate of 2-bromo-1-(4-nitrophenyl) ethanol (3) as shown in Fig. 2. The racemate was then transesterified enzymatically.

A simultaneous process was developed. As described in Fig. 2, the (S)-(+)-sotalol (6) and (R)-(−)-nifenalol (7) were prepared from the enantiomers separated enzymatically from the compound 3. The (S)-bromo ester was used to form the (S)-6, whilst the (R)-bromo alcohol gave the (R)-(7). The route reduces the unused enantiomers.

Several reactions took place at low temperatures. Formation of the racemic 2-bromo-1-(4-nitrophenyl) ethanol (compound 3) occurred at 0 °C. Temperature of −20 °C was used to hydrolyse the remaining epoxide in the (R)-nifenalol synthesis [146]. Racemic 2-hydroxy-4-(4-methoxy phenoxy)-butanoic acid methyl ester, the substrate for lipase catalysed reaction, was prepared at −70 to −30 °C [40].

The enzymatic resolution was performed to resolve the chiral intermediates through hydrolysis of the racemic acetate or trans-

Table 2
Chemo-based catalysis of single enantiomeric β-blockers.

Drug	Starting material(s)	Asymmetric catalyst/addendum	Yield (%)	ee (%)	Conditions T (°C)	Conditions t (h)	Ref.
	Oxirane derivate	(R,R)-[Co(salen)]	32–40	70–99	rt–reflux	5–8	[79]
	Epichlorohydrin, 1-naphthol	Zn(NO$_3$)$_2$ + (+)-Tartaric Acid	94	89	rt–40	6–24	[120]
PRO	Allyl Bromide, 1-naphthol	[Rh(1,5-cyclooctadiene)Cl]$_2$, (2S,4S)-MCCPM	98	90.8	0–50	1–20	[121]
	Allyl Bromide, 1-Naphthol	[Rh(1,5-cyclooctadiene)Cl]$_2$, (2S,4S)-MCCPM	98	90.8	0–50	1–20	[122]
Metal–ligand catalysts							
	Phenol derivates	Ti(IV)isopropoxide + (+)-DIPT	48–70	ND	(−25)–rt	0.5–5	[123]
BIS, PIN, OXP, PRO	Propylene oxide, TMSN3	(R,R)-(salen)CrN$_3$	ND	ND	0–2, ND	18–50, ND	[124]
	Phenol derivates	CsF, (S)-Glycidyl Nosylate	83–95	98.8–99.8	5–25	6–24	[125]
Many beta-blockers	Phenol derivates, allyl bromide	OsO$_4$, (DHQD)$_2$-PHAL	70–99	ND	Reflux, 0–25	0.5–12	[126]
NEB	6-Fluorochroman-2-one	LDA, (R)-methyl-p-tolyl-sulfoxide, (S)-methyl-p-tolyl-sulfoxide	11.5 (overall)	>99	(−78)–rt	ND	[127]
	p-Fluorophenol, allyl bromide	Ti(IV)isopropoxide + (−)-DET, (+)-DET	20 (overall)	ND	Reflux, (−20)–210	0.5–10	[128]
	Allylic epoxide	(R)-(EBTHI)Zr-Binol	10.9 (overall)	ND	(−78)–70	0.2–24	[129]
BIS	Phenol derivates	CsF, (S)-Glycidyl Nosylate	90	98.8	rt–50	0.5–18	[130]
DCI, PRN	Oxathiane, tifluoromethane sulfonic	LiAl(NHiPr)$_4$	50–77	ND	(−10)–40	1–48	[131]
NAF	Epichlorohydrin, 1-naphthol	(R,R)-salen Co(III)OAc complex	93	ND	rt–100, reflux	5–30	[132]
NIF	α-Sulfonyloxy-ketones, N-ethyl-N-isopropylaniline-borane	(R)-methyl-CBS-oxazaborolidine	93	>99	25, rt	0.17–5	[133]
Organocatalysts							
PRO, NAF	1-Napthol, 3-bromopropanol	L-Proline	26 (overall)	ND	(−20)–rt, reflux	0.5–24	[134]
SOT	4-(Chloroacetyl)methane sulfonanilide	(S)-methyl-CBS-oxazaborolidine	58.3	98	rt–130, reflux	0.5–18	[135]
PRO	1-Naphthol	(2S)-Tosylate	27	ND	25–reflux	1–24	[136]
BIS	4-Hydroxybenzyl alcohol, 2-isopropoxy ethanol, epichlorohydrin	(S)- and (R)-Glycydil tosylate	36 (overall)	99	rt–100	2–18	[137]

ee: enantiomeric excess; *T*: temperature; *t*: time; ND: no data; rt: room temperature; NAF: naftopidil; PRN: prenaltelol.
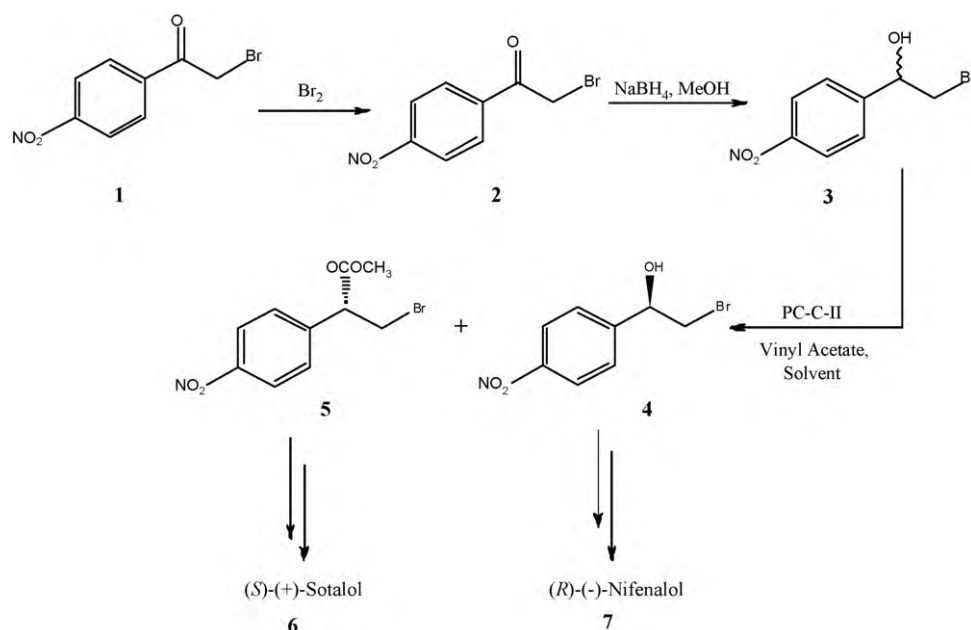
Fig. 2. Chemo-enzymatic process of (S)-(+)-Sotalol and (R)-(−)-Nifenalol.

esterification of the racemic alcohol at moderate temperatures (Table 3). Excellent ee was resulted, however, long reaction times were required. Free form *Pseudomonas cepacia* lipase (PCL) gave higher enantiomeric ratio and shorter reaction time compared to lipases from *Porcine pancreas*, *Candida rugosa*, *Chromobacterium viscosum* and *Rhizomucor miehei* [40]. Immobilised PCL on diatomite produced higher ee and good yields than the PCL immobilised on ceramic particles (PS-C), immobilised *Mucor meihei* lipase (Lipozyme) and its free form [37].

3.3. Chemo-enzymatic dynamic kinetic resolution

To overcome the kinetic resolution drawback, dynamic kinetic resolution (DKR) is developed. As the previous technologies, this process exploits many chemical catalysts and a biocatalyst in the sequential reactions. The DKR combines the enzymatic kinetic resolution of the racemic substrate with *in situ* chemical racemisation of the undesired enantiomers [148]. During the process, the racemic substrate is split enzymatically to form the desired enantiomer wherein the undesired enantiomers are racemised chemically to give the racemic mixture then resolved again by the enzymatic resolution. The process provides higher results, but it is rarely applied to produce the single enantiomeric β-blockers.

The (S)-propranolol was prepared by the technology [149]. The one-pot DKR of racemic azido alcohol was conducted by employing Novozyme 435 lipase and *p*-chlorophenyl acetate, and a ruthenium compound as the racemisation catalyst. This step produced azido acetate in 71% yield and 86% ee. Hydrolysis of the acetate with lithium hydroxide in methanol at room temperature followed by azide reduction and *in situ* reductive alkylation using Adam's catalyst in the presence of acetone at the same temperature gave the (S)-propranolol in almost enantiomerically pure form.

3.4. Whole-cells reduction

Whole-cells are used to replace the enzyme function in reduction of the racemic substrates. This process would be advantageous in resolution of the racemic compounds since the cells contain redox enzymes that catalyse reduction and oxidation steps [150,151]. The cells also have multiple dehydrogenases, which are useful for non-natural substrates, all the necessary co-factors and the metabolic pathways for their regeneration [152]. It is used for reactions that require multiple enzymatic steps and/or cofactor recycling [153] and a cheap alternative [154]. The process gave higher yield than the enzymatic resolution results. It had to be integrated to the chemical catalysis to make the single enantiomers.

Reduction of the prochiral or racemic substrate(s) microbially produced medium to high yields (36–100%) and ee (49–97%) at mild operating temperatures (27–30 °C) in 5–96 h fermentation time [144,152,155]. In general, the isolated yields of the single enantiomeric β-blockers were less than 50%. Type of substrate and microbe influenced the process performance. Yang et al. [152] found the reduction products differed in the enantiomeric configuration, although the aromatic ketones, acetylpyridines or α- and β-ketoesters were fermented by the same microbes. Iriuchijima et al. [155] comparing 250 microorganism types concluded that *Mucor* species hydrolysed the racemic substrate enantioselectively, but they produced lower selectivity than pancreatin or steapsin.

3.5. Chiral pool strategy

The final way to make the single enantiomeric β-blockers asymmetrically is developed by the chiral pool synthesis [137]. The process prepares the optically active complex compounds from a stockpile of readily available enantiomerically pure/homochiral molecules [156,157], which could be synthetic intermediates or natural products [158–160]. It requires fewer reaction steps [161], involved no chiral catalyst and no racemates in the reactions. Performance of the process is given in Table 4. Only chemical catalysts were found being used. High yields were obtained at low to medium operating temperatures and short reaction times. Most of the starting materials were derived from D-mannitol.

4. Resolutions of the existing racemic β-blockers

The resolution processes mainly separate the racemic compounds into their single enantiomers. They use the racemic β-blockers or their esters or diastereomeric derivates as substrates. Although they produce high ee, the processes are frequently limited by 50% yield. Some processes are success at analytical levels.

Table 3
Chemo-enzymatic process of single enantiomeric β-blockers.

Drug	Starting material(s)	Chemical Part			Enzymatic part						Ref.
		T (°C)	t (h)	Yield (%)	Substrate/enzyme		T (°C)	t (h)	Yield (%)	ee_p (%)	
ALP, MOP, PRO	Epoxides, NaCN	25–30	1–18	80–90	rac-β-Hydroxynitriles	PSL	20–40	9–48	43–46	92–99	[38]
	2-Aryloxy-acetic acid ethyl esters	(−70)–90	2–4	79–100	rac-3-Hydroxy-ester	PCL	ND	22	50	98	[40]
PRO	1-Naphthol + epichlorohydrin	5–90	1–24	90–94	rac-1-Chloro-2-acetoxy-3-(1-naphthyloxy)propane, rac-1-chloro-3-(1-naphthyloxy)-2-propanol	PSL	rt	ND	ND	ND	[41]
	1-Naphthol + 1,3-dichloropropanol acetate	0–Reflux	3–12	72–97	rac-1-Chloro-2-acetoxy-3-(1-naphthyloxy)-propane	CCL	rt	ND	50	ND	[143]
	3-Chloro-1,2-propanediol	0–Reflux	0.2–12	52–92	rac-1,2-Diacetoxy-3-chloropropane	PSL	25	17	20	90	[144]
SOT, NIF	4-Nitroaceto-phenone	0–35	2–12	70–90	rac-2-Bromo-1-(4-nitrophenyl) ethanol	PSL; C II	28	28	50	>99.5	[145]
NIF	rac-p-Nitro-styrene-oxide	ND	20–24	90–94	rac-p-Nitro-styrene-oxide	A. niger	25	26	ND	ND	[146]
PRT	3-(4-Acetamido phenoxy)-1,2-epoxypropane	rt	2.5	ND	1-Chloro-3-(-acetamido phenoxy)-2-propa nol acetate	LAPS	rt	ND	ND	>98	[147]

ee_p: product enantiomeric excess; T: temperature; t: time; ND: no data; rt: room temperature; PRT: practolol; rac: racemic.

4.1. Enantioselective extraction

It is defined as separation of a component dissolved in an immiscible liquid by treatment with an immiscible solvent in which the desired component is soluble [165]. The process is a good alternative. The extraction has high interfacial area [166], separates selectively and reversibly and can be enhanced by using the extractant(s) [167]. In resolution of the β-blockers, two extraction types were developed. Both processes required chiral selector(s) added to one of the two immiscible phases [168]. The selector reacted with one of the enantiomers forming an enantiomer-chiral selector complex; hence the chiral molecules could be separated.

The biphasic extraction was based on direct contact between the compounds and solvent. Its recent study was used to split the racemic propranolol using the (R)- and (S)-di-n-dodecyl tartrate. Formation of the (R)-propranolol-borate-(R)-di-n-dodecyltartrate complex separated the racemate in which the (S)-propranolol dissolved in the aqueous phase. Enantioselectivities (α) of 1.3–2.8 and ee of 3.0–14.9% at pH 4.4–5.6 was obtained [177]. Previously, (S,S)-di-n-dodecyltartrate was employed [169]. The agent dissolved in chloroform was mixed with the pH 5.2 aqueous phase consisting of propranolol, demineralised water, boric acid and acetate buffer. The process resulted 1.0–9.3% ee. The liquid phases, temperature and length of the alkyl chain influenced the α [170].

The second extraction type operated permeable membrane(s) used to separate both phases. Formation of the enantiomer-chiral selector complex took place at the membrane surfaces. The unwanted enantiomer was transported from the aqueous to the solvent phase. Highly lipophilic chiral selector(s) was operated to avoid transport of the chiral selector over the membrane [171]. In this process, extraction and stripping of reaction product(s) could run simultaneously.

A recent study was performed in a membrane contactor applied to resolve the racemic propranolol using (R)- and (S)-di-n-dodecyltartrate [172]. The aqueous phase (boric acid and racemic compound buffered with acetic acid and sodium acetate) and organic phase (chiral selectors in chloroform) were contacted in tubular ceramic membranes. The process gave ee and selectivity of 40% and 2.3 (single extraction), 69% and 2.3 (simultaneous extraction), 57% and 2.9 (extraction and stripping) and 92% and 2.9 (simultaneous extraction and stripping). Another experiment used the (R,R)- and (S,S)-dihexyltartrate [171]. An aqueous phase of the racemic propranolol and phosphate buffer-citric acid were mixed with heptanes consisting of these selectors. Selectivity of 1.03 was obtained.

4.2. Whole-cells transformation

As stated previously, the whole-cells are used to resolve the racemic mixtures. In the last decade, only one article is published using this technology. It resolved the racemic propranolol using *Rhizopus arrhizus* and *Geothricum candidum* giving good optical purities and chemical yields [95]. Two ways were developed i.e. direct and indirect resolution in which the direct process produced higher results. In the direct resolution, the racemate was fermented with the cells for 6 days at pH 7.0. After purification and separation of the broth, the resolution gained the (S)-(−)-propranolol in 78–88% ee and ±74% yield. Another method required the propranolol be acetylated initially. Then the racemic acetates were cooked for 6 days at pH 7. The (S)-(−)-propranolol was recovered in ±70% yield and 39–68% ee.

4.3. Enzymatic kinetic resolution

The racemic β-blockers can be resolved by the stereoselective enzymes [173]. Direct resolution can be conducted by transesterifi-

Table 4
Single enantiomeric β-blockers synthesis using chiral pool.

Drug	Starting substrate	Reactions		Final yield (%)	ee (%)	Ref.
		t (h)	T (°C)			
PEN, CRT, PRO, PRE, MOP	(S)-5-hydroxymethyl-3-alkyl-2-oxazolidinone	1–15	rt-80	53–70	96–100	[84]
OXP	(2S)-3-tosyloxy-1,2-propanediol acetonide	5–120	0-110, reflux	24	ND	[158]
PRO	(S)-(−)-1-(2,3-dihydroxy propoxy)-naphthalene	2–20	22-reflux	95.6	ND	[161,162]
	(R)-(−)-2,2-dimethyl-4-napthyloxy methyl-1,3-dioxolane	0.5–1	ND	79.6–81	ND	
PRO, CRT, PIN	(2R)-2,3-O-isopropylidene glyceraldehyde	0.5–12	0–120, reflux	ND	ND	[163]
PRT	(R)-(−)-α-(4-toluenesulfonyl) acetone glycerol	0.5–72	5–75	ND	ND	[164]

ND: no data; rt: room temperature; t: time; h: hour; T: temperature.

cation reaction [174] or hydrolysis of the ester(s) with high ee [175]. The method has been detailed in the previous articles [73,173].

4.4. Liquid chromatography-based processes

Separation of compounds is based on adsorption of solid or partition to a stationary or bonded liquid phase [176]. The processes are designed by many columns, chiral stationary phases and/or solvents and modifiers in batch or continuous operations. Several types of LC-based processes have been related to separation of the β-blockers.

4.4.1. Simulated moving bed (SMB)

The main characteristic of SMB is continuous counter-current movement of the stationary and mobile phases [177] where the simulated movement is created by periodic switching of injection and withdrawal ports along the columns in direction of fluid flow [178]. It is highlighted as one of the most promising method for enantioseparation [34].

The SMB achieved high purity β-blockers in short times based on polysaccharide chiral stationary phase [179,180]. It was capable to separate the β-blockers with more than one chiral centre. The performance was affected by the number of contacting zone and column configuration (number of operating column in each zone). For example, in the 4-zone SMB, the column configuration of 1/2/1/1 was superior to that with 1/1/2/1 in achieving higher purity of the raffinate and extract, and the Varicol operation with the configuration of 1.5/1.5/1/1 showed better performance over the traditional SMB process [178]. In separation of a ternary mixture, such as the racemic nadolol, operating a single 5-zone SMB gave high purity and yield rather than using two 4-zone SMB units [179].

4.4.2. Chiral belt chromatography

The process used a rayon belt coated with tris-(3,5-dimethylphenyl carbamate) (CTPC) to convey an enantiomer. The belt, which rotated continuously, was contacted to the solvent containing a chiral compound. The enantiomer was adsorbed and carried-out of the solvent by the belt during its rotation.

Works on the chiral belt chromatography were started by studying the CTPC-coated membrane performance batch-wise [181]. A single adsorption-desorption of the CTPC-membrane gave β-blockers with up to 60% ee. The membrane was then developed into a chiral belt unit, which treated the racemic oxprenolol [182]. After series of solvents-contacting and belt-rinsing steps, ee up to 68% was obtained.

4.4.3. High performance liquid chromatography and other methods

The high performance liquid chromatography (HPLC) resolved the racemic β-blockers by employing different detectors [74] either directly or indirectly [51] using different types of column [183–187]. Others developed super-critical fluid, nano-liquid chromatography, capillary liquid chromatography, thin layer chromatography and gas chromatography [188–196]. Overviews of the HPLC-based separation could be found in the previous articles [77,197].

4.5. Electromigration techniques

These techniques are a powerful alternative in the chiral separation [198]. They provide high capability with minimum solvent and reagent consumption [199]. In the β-blockers separation, two techniques are developed: (a) Electrophoresis and (b) Electrokinetic chromatography. Various voltages and chiral selectors have been tested, which produce good resolution factors at relatively short times and mild operating temperatures.

Chiral separation using the electrophoresis is based on different electrophoretic mobilities of solutes [200]. It exploits movement of charged species under the influence of electrical field. The process is performed directly using chiral selectors or indirectly employing chiral derivatization agents forming diastereomeric pairs [201]. The direct method is frequently used and has resolved the compounds efficiently [74]. Performance of the process is given in Table 5. The process was capable to separate the single and multiple stereogenic centres β-blockers [202]. Three processing types were established: capillary zone electrophoresis (CZE), electrokinetic chromatography (EKC) and ligand exchange capillary electrophoresis (LECE). Although traditional electrophoresis was frequently used, modified methods had been introduced. These involved application of the chiral ligands and molecularly imprinted polymer (MIP) as the chiral selectors. The chiral ligand showed excellent enantioselectivities [96]. The MIP produced similar results, but required structure modification in the background electrolyte [212].

The CZE separated the compounds directly where the chiral selector was added to the background electrolyte or bonded to either the capillary wall or a stationary phase [205]. In resolution of the racemic β-blockers, it resolved the racemates rapidly by operating thousands volts of electrical powers and aqueous-based electrolytes. Type and concentration of the chiral selectors and pH of the background electrolytes had strong effects on the process [82]. Addition of organic modifier to the electrolytes enhanced the process [206]. It was found that the charged chiral selectors were more effective than the neutral type [80,95]. The charged selectors gave good resolution values at low pH (2–8). Separation based on non-aqueous capillary electrophoresis (NACE) was also performed. This process was affected by alkali metal hydroxide presenting in the electrolytes [213]. The factors of 2–10 were obtained [214]. The results showed a complex formation between the solute and selector [215].

The EKC combines principles of chromatography and capillary zone or free solution capillary electrophoresis for the separation [216]. In contrast to the CZE, the EKC worked at high pH using either natural or synthetic chiral polymers. Two EKC types were developed: affinity EKC (AEKC) and micellar EKC (MEKC). The AEKC used proteins as the chiral selector. It presented good and unique inter-

Table 5
Electromigrating-based resolution of racemic β-blockers.

	Drug	Volt	Chiral selector	Electrolyte	Capillary	T (°C)	Resolution factor	Time (min)	Ref.
	Many beta-blockers	25,000	Cyclodextrins	Phosphate buffer, pH 2.5–5.5	Silica, 50 μm ID, 43.3 cm L	15	1.21–11.95	6–24	[31]
	Many beta-blockers	10,000–18,000	Cyclodextrins	Phosphate buffer, pH 2.5 and 4.4	Silica, 50 μm ID, 26 and 39 cm L	20	0.53–2.05	8–60	[45]
CZE	SOT, BIS, BEV	10,000	Cyclodextrins	Acetate, Phosphate buffer, pH 4–7	Silica, 75 μm ID, 37 cm L	ND	1.10–2.50	13–24	[80]
	PRO, ISP, ART	30,000	SO4–Cyclo sophoraoses	Phosphate Buffer, pH 3	Silica, 50 μm ID, 33 cm L	25	0.25–1.11	35–53	[95]
	LAB	30,000	Cyclodextrins	Phosphate buffer, pH 2.5	Silica, 50 μm ID, 56.4 cm L	25	ND	15	[202]
	ESM	12,000	Cyclodextrins	Phosphate buffer, pH 2.5	Silica, 50 μm ID, 48 cm L	32	0.50–3.10	ND	[203]
	OXP, PRC	15,000	Cyclodextrins	Britton-Robinson, buffer + modifier	Silica, 50 μm ID, 60 cm L	ND	0.70–1.20	11–29	[204]
	PRO, PIN	20,000–30,000	Cyclodextrins	Phosphoric acid, buffer + TEA	Silica, 20 + 50 μm ID, 48.5 cm L	15	1.43–2.51	21–58	[205]
	LAB, NAD	15,000	Cyclodextrins	Phosphate buffer, pH 2–8	Silica, 50 μm ID, 40 cm L	30	0.50–4.70	16–45	[206]
	Many beta-blockers	261 or 298 V/cm	Cyclodextrins	Phosphoric acid, buffer + TEA	Silica, 50 μm ID, 30 cm L	20	0.41–11.20	2–15	[207]
AEKC	PRO, OXP	20,000	Bovine Serum Albumin	Phosphate Buffer pH 6.9	Silica, 50 μm ID, 58.5 cm L	15	0.4–1.1 1.0–1.1	10	[208]
	OXP	15,000	Human Serum Albumin	Tris-(hydroximethyl)–aminomethane pH 8.5	Silica, 50 μm ID, 65 cm L	30	0.2–1.6	8	[209]
MEKC	Many beta-blockers	12,000	N-dodecoxy carbonylvaline	CHES, HEPS buffer, pH 8.8 + TEA + NaOH	Silica, 75 μm ID, 52–55 cm L	25	1.03–1.08	20	[210]
	NAD, LAB	20,000	Poly-L-SUCL, Poly-L-SUCIL	CHES buffer pH 8.8 + TEA + NaOH	Silica, 50 μm ID, 64.5 cm L	25	0.39–2.08	ND	[211]
	Many beta-blockers	20,000	Poly-L-SUCL	CHES buffer pH 8.8 + TEA + NaOH	Silica, 50 μm ID, 57 and 64.5 cm L	ND	0.83–3.30	ND	[94]
LECE	Many beta-blockers	10,000	L-Tartaric acid or L-Threonine + Cu(II) sulphate, pH 12		Silica, 50 μm, 65.5 cm L	25	0.58–1.11	15–20	[94]
	Many beta-blockers	15,000	N-(2-hydroxy-octyl)-L-4-hydroxyproline + Cu(II)sulphate + TEA, pH 12		Silica, 50 μm, 70 cm Length	ND	0.72–2.22	5	[96]
CEC	OXP, PIN, PRO	30,000	Octadecyl silanised	Sodium borate pH 8 + ACN (Acetonitrile)	Silica, 75 μm ID, 32 cm L, 8 bar	25	0.50–1.81	3–26	[99]
	OXP, PRO	25,000	Vancomycin	Ammonium Acetate pH 6, Methanol + ACN	SILICA, 75–100 μm ID, 10 bar	ND	0.55–1.89	8–10	[100]
	PRO, PIN, ALP	10,000	Vancomycin	Methanol + ACN + Acetic acid + TEA	Silica, 50 μm ID, 15 cm L, 20 bar	25	1.08–2.01	3–4	[101]
	PRO, ISP, ALP	15,000	Cyclodextrin	Methanol + Phosphate buffer, Methanol + TEAA	Silica, 75 μm ID, 18, 55 bar	ND	0.57–2.48	5–15	[221]
	PIN	25,000	Cellulose	Phosphate buffer + ACN	Silica, 100μm ID, 24 cm L, 8 bar	25	2.32	2–6	[223]
	PRO, PIN	171–357 V/cm	Cyclodextrin	Boric acid buffer pH 9 + TRIS	Silica, 75 μm ID, 60–70 L	25	0.93–1.90	39–49	[224]

BEV: bevantolol; ISP: isoproterenol; CHES: 2-[N-cyclohexylamine]ethanesulfonic acid]; HEPS: 4-(2-hydroxyethyl)-1-piperazineethane sulfonic acid; SUCL: sodium N-undecenoxy carbonyl-L-isoleucinate; SUCIL: sodium N-undecenoxy carbonyl-L-leucinate; TEA: tri-ethyl amine; NaOH: sodium hydroxide; ND: no data available; ID: inside diameter; L: length; TEAA: triethylammonium acetate.

Table 6
Technologies for replacement of the racemic β-blockers.

Existing routes	Operation mode		Single enantiomeric yield	ee
	Batch	Continuous		
Chemocatalytic synthesis	√	×	Medium–High	High
Chemoenzymatic synthesis	√	×	Medium–High	High
Dynamic kinetic resolution	√	×	Medium	Medium
Whole-cells	√	×	Medium–High	Medium–High
Chiral pool synthesis	√	×	Medium	(Insufficient data)
Enantioselective extraction	√	√	≤50%	Low–High
Liquid chromatography processes	√	√	≤50%	Medium–High
Electromigration techniques	√	√	≤50%	(no data)
Enzymatic kinetic resolution	√	×	≤50%	High

actions between the enantiomers and protein [208]. The MEKC used micelles as the dispersed phase [217]. The polymers were capable to resolve the β-blockers with more than one chiral centre [211,218]. Chiral LECE was conducted by employing a chiral selector–metal complex as an additive [219]. Similar to the EKC process, the LECE worked at high pH values to form the complex molecule(s).

In capillary electrochromatography (CEC), the mobile phase and analytes are pumped through the column by electro-osmotic flow generated by application of a high electric field [92]. The CEC is considered as a separation technique combining the liquid chromatography and capillary electrophoresis. It provides improved efficiency over the liquid chromatography with the same stationary phase [220]. The CEC has separated the β-blockers rapidly. The resolution factors of 0.50–3.80 were resulted. A quick separation could be achieved by utilising the molecularly imprinted microparticles or non-aqueous mobile phase [101,220–222]. The process was influenced by the organic modifier added to the aqueous buffer [100,102].

4.6. Diastereomeric formation (DF)

The technology has been practiced at large scales for years [225]. It is based on differential interaction of a racemate with a chiral resolving agent forming a pair of diastereomers, which can be separated by achiral methods [226]. The technology is covered by the extraction, indirect chromatography and crystallisation operation.

5. Perspectives on the existing processes

Two alternatives are related to the efforts to replace the existing racemic β-blockers: employing the chiral switches or constructing the new synthetic pathways. Both alternatives have used the chemical, biological or combination of the agents. A comparison of the existing processes is shown in Table 6. Most of the processes operate batchly. Some processes produce high yields, other methods are limited by 50% yields.

The asymmetric syntheses give outstanding choices. The new routes are developed through chemo, chemo-bio or microbial way(s). Excellent (medium-high) yields and high ee are reported. The routes introduce new substrates either racemates, chiral molecules or inactive substances. Novel molecules are established in the reactions. The syntheses have involved the newest technique applied to the chiral drugs i.e. the dynamic kinetic resolution, which offers a new way to resolve the distomers and overcomes the kinetic resolution drawback.

Many asymmetric synthetic processes use temperatures below 0 °C (−20 to −78 °C). To obtain the low temperatures, a cooling/refrigeration system completed with a regeneration unit for the cooler/refrigerant should be available. The materials of construction for the systems (piping, reactor, etc.) must be tolerant to the low temperatures. To get the required temperatures, it is not only costly in terms of cooling, but also presents problems associated

with materials of construction and removal of the heat associated with exothermic reaction(s) [227]. The syntheses develop the products from the raw materials. This means many reactions should be conducted and many intermediate compounds should be handled. They finally require many steps and development of appropriate paths for the each product. These steps increase complexity of the processes and lead to considerable costs and long development periods [170,172,227]. The asymmetric resolution of the corresponding racemates, asymmetric lipase-catalysed kinetic resolution, which is limited by the maximum yield of 50%, and the chiral pool method have high operational costs and multiple steps. They are difficult to be applied to large-scale production [228]. The use of poisonous chemicals and multiple procedures make these processes costly. Many of the metal catalysts are expensive and toxic compounds: loss of the metal ligands during the separation and purification steps of the intermediate precursors could burden the processing costs and their presence in the final products would present a potential toxicological problem [229]. Although the DKR has given high yield, it is still a novel method in the β-blockers preparation. The technology in fact had developed (*S*)-ibuprofen, (*S*)-fenoprofen, (*S*)-naproxen, (*S*)-suprofen [230], diltiazem [231] or (*R*)-bufuralol [232] effectively. A maximum theoretical yield of 100% could be obtained. But it requires compatibility of the kinetic resolution and racemisation step [233,234]. Though the asymmetric syntheses produce low overall yields and other limitations should be considered in the development, they indeed offer a broad range of oriented alternatives.

The second alternative consumes the available racemates. It is based on separation of the enantiomers except the whole-cells biotransformation. The existing processes have employed continuous based-operation. Many chiral agents/selectors are explored. They work at mild operating temperatures compared to the first alternative. However, performance of the processes is generally limited by 50% yield. This means only half of a racemic mixture will be used to form the single enantiomeric compounds; the other part is useless.

The traditional extraction uses the biphasic direct contact method. This process indeed needs further exploration because it produced very low ee. Besides, it must be integrated to the organic phase regenerating system for its nonstop use. The advanced extraction operates *in situ* separation by functioning membrane modules as filters of the enantiomers. The modules provide large surface areas for contact and separation. Their use offer advantages over the traditional way such as low cost, simplicity of operation and easy scale-up [235]. Stability of the supported liquid membranes in industry is the major drawback [236]. Both processes need to separate the chiral selector from the phase containing one of the enantiomers of the resolved racemate.

Although the liquid chromatography is a superior analytical technique, the method has tedious sample preparation procedures, expensive chiral columns, large volumes of eluting solution additives and time consumption [80]. Regeneration of the solids in the
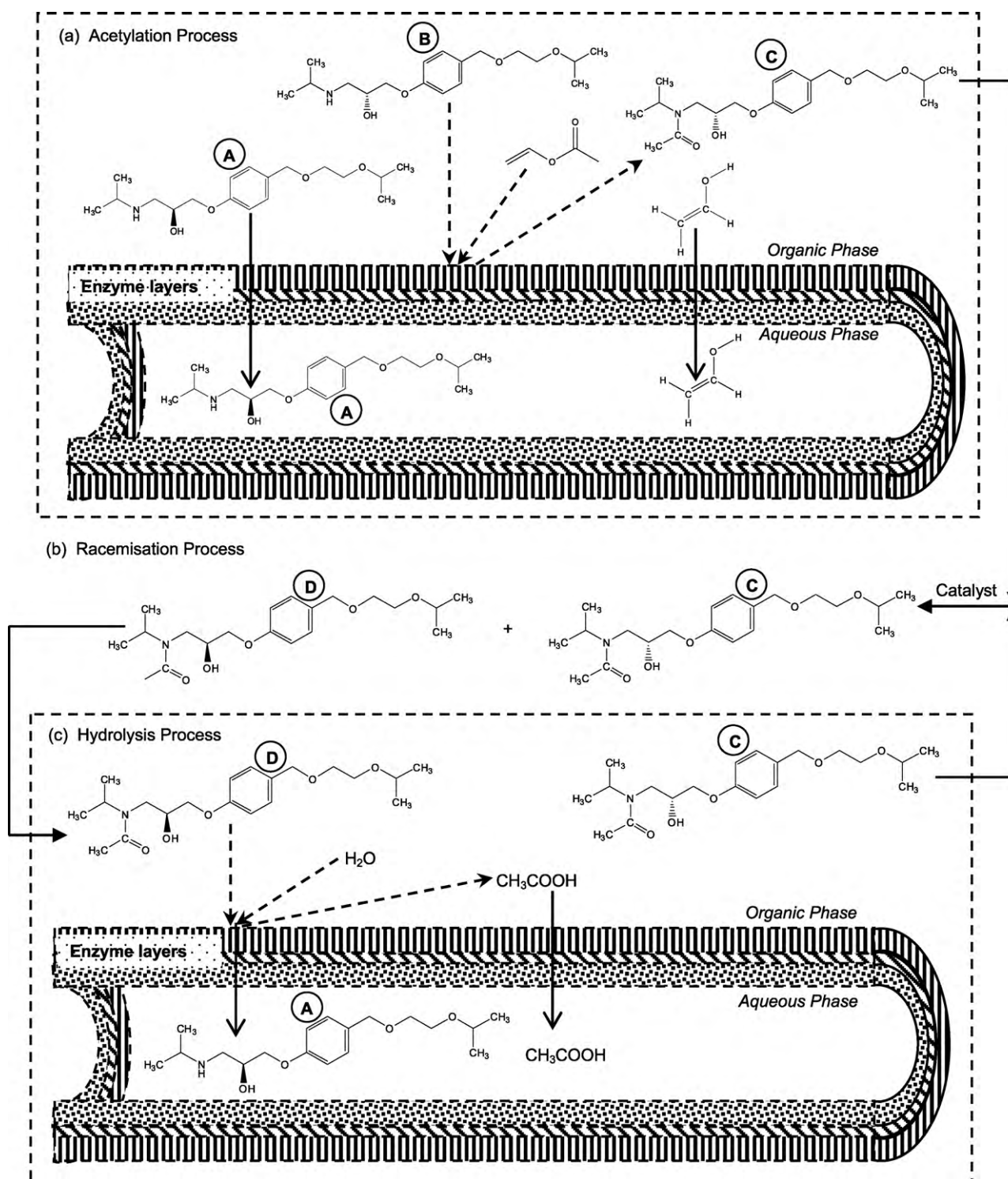
Fig. 3. Dynamic kinetic resolution of a racemic β-blocker: (a) Acetylation process, (b) Racemisation process, (c) Hydrolysis process.

SMB process is required in order to use the columns continuously. The desorption process demands more capillary columns if the desorption is difficult and needs eluting solution. Besides, the solution should not contain solid particles, which could block the capillary columns. Also the SMB has pressure limitations and needs accurate controls of the product flow rates [21]. While the chiral belt operates continuously and requires no separated regeneration step, it still requires the eluting solution and a proper procedure for immobilisation of the selector. The HPLC and electromigration techniques are very useful in analysis. Many of them are still exploratory techniques as can be concluded from the number of studies [237], besides the analytical techniques, even though available for all racemates, are not adequate to large-scale [227,236].

Formation of the diastereomers is one of the oldest methods in the β-blockers separation [51]. The technology requires derivatization of the enantiomers [238]. A step to form the diastereomers should be integrated to the process, which means an additional step should be available before the resolution is carried-out. Although

the extraction processes are applicable in large scale, they produce low ee except the extraction and stripping membrane-based process. The crystallisation of the diastereomeric molecules needed development of an appropriate path for each product leading to many processing steps [227,236]. Moreover, the method is more favourable for the determination of enantiomeric drugs in biological specimens [239]. It might suffer from extra burdens with respect to validation of the total analysis method [240].

Although the enzymatic kinetic resolutions give high ee, the process generally produces less than 50% yield. Either free or immobilised enzymes are employed in the resolutions, which are predominantly carried-out in a one-pot batch type reaction. Hence, a sort of recycle system for the enzyme should be available if an expensive enzyme is used. This is also found in the whole-cells processes. Even though the whole cells are economical and operationally simple [84] and give high yield and ee, preparation and recovery of the cells should be considered.

Many alternatives are provided by the syntheses, which orientate to the raw materials and catalysts development. The resolution ways are a faster strategy because the drugs are available in the markets. Adoption of a new resolution based-process expected to give high yield and ee and operating continuously is considered. The DKR process certainly offers a better way in the racemic resolutions. It is an efficient technique producing enantiomerically pure form of the intended products [230]. Application of the DKR process in the membrane modules, which provide large contact surfaces and separate the mixture(s), is a prospective choice.

6. Chiral switch via dynamic kinetic resolution using enzymatic membranes

Since there is no single effort to resolve the racemic β-blockers using enzymatic membrane reactors (EMRs), the EMRs-based resolution is encouraged. The EMRs combine enantio selective properties of biocatalyst and separative properties of membranes; hence conversion and separation of enantiomers are integrated into a single step [241,242]. Compared to other technologies/enzymatic reactors, they have advantages such as development of continuous operation, high productivity and stability, better control possibilities, improvement of rates in product-inhibited reactions, enrichment and concentration of products in process streams [66,243]. Many EMRs studies point out that this technology is one of the best approaches [244]. Hence, they are now increasingly being used due to efficacy of the enzymatic resolutions and simple reaction conditions [245].

The dynamic kinetic resolution gives better prospects. It deals with the only problem faced by kinetic resolution (KR): it increases yield above the KR limit; so that the untreated enantiomers decrease. It produces excellent conversion and ee. Racemic alcohols, amines, esters and acids had been resolved giving 45–99% yields and more than 99% ee [230] using lipases/microorganisms and organic/inorganic chemical catalysts in organic-based solvents.

A DKR scheme for the racemic β-blockers is shown in Fig. 3. Three reactions occur in the system: acetylation, chemical racemisation of distomers and hydrolysis. Initially, the enzymatic acetylation is carried-out. The enzyme immobilised on the membrane surfaces catalyses reaction of the racemates dissolved in an organic phase with an acetyl compound. For example, target of the DKR is the (S)-β-blocker (A). The racemate is fed to the (R)-preference enzyme so that the (R)-enantiomers (B), which react fast, are changed to the (R)-acetyl-β-blocker (C). This reaction can be observed in Fig. 3a. The substrate (B) has to be transported across the membrane to the catalyst sites and the target compound (A) is moved from the reaction sites to the other sides of the membrane [246]. The (S)-β-blocker accumulates in the aqueous side

because of the transmembrane pressure. This reaction has been studied batchly producing good conversion and ee [174,247]. Resolution of other alcohols in organic solvents using the acetylation at moderate batch temperatures gave conversion of 3–68% and ee of 2–99% [248–255].

Secondly, the (R)-acetyl-β-blocker (C) is racemised in the organic phase: one stereoisomer will become a mixture of equal amounts of each enantiomer [256] i.e. the racemic acetyl-β-blocker (C and D) as drawn in Fig. 3b. Various metal-complex, acid and base catalysts had been studied in aqueous or organic solution [257–259]. The final step is to hydrolyse the racemic acetyl-β-blocker. The racemate is fed to the (S)-preference lipase. As shown in Fig. 3c, the racemic compound available in the organic phase is contacted to the enzyme immobilised on the membrane surface. The (S)-acetyl-β-blocker (D) is hydrolysed to the (S)-β-blocker enantiomers (A). The reaction products flow to the aqueous phase because of the transmembrane pressure. The enzymatic hydrolysis of racemic esters batchly using the hydrolytic lipases in phosphate buffer or organic solvents at low to moderate temperatures produced yield of 2–68% and ee of 30–99% [260–267]. Resolution of racemic drugs esters enzymatically in inorganic membrane reactors resulted conversion in the range of 0.74–31% and ee of 68–100% [268–270].

Some aspects of the DKR such as irreversible reaction, compatibility of the kinetic resolution and racemisation procedures [233,234] should be considered. The main challenge in an efficient DKR is finding suitable substrate racemising conditions that do not adversely affect the enzyme resolution or interfere with the chiral integrity of the product [148]. Due to enzymes are very active on hydrophilic interfaces, the EMRs are developed using hydrophilic membranes, although the hydrophobic membranes are more physically and chemically stable [271]. The hydrophilic membranes provide thick contact zone, water-wetted interfaces, high enzyme activity and low enzyme concentration [272].

7. Conclusions

Many processes to replace the existing racemic β-blockers into single enantiomers have been reported. The asymmetric syntheses, the first category, give an outstanding choice. Medium to high yields and great ee are produced. Their chemo, chemo-bio or microbial way(s) utilise various substrates and catalyst types. Novel molecules are found within its pathways. Simultaneous processes are also established. The technology indeed offers a broad range of oriented alternatives to the single enantiomeric β-blockers preparation. The second group, the racemic resolutions, comes with many attractive methods. Direct or indirect processes have shown excellent characteristics and are capable in giving high ee. They are operated continuously and work at mild operating temperatures. *In situ* separation of the enantiomers has been developed. Performances of the processes are generally limited by 50% yield. Several techniques are not adequate to large-scale production. Both groups have utilised new techniques in the single enantiomer preparation such as the asymmetric dynamic kinetic resolution and membrane-based extraction. Application of the dynamic kinetic resolution for the racemates using enzymatic membrane reactors is a new way to resolve the drugs. Integration of the acetylation, racemisation and hydrolysis steps followed by separation of the target enantiomers in the membrane reactors could be a better option in resolution and separation of the β-blockers.

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