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HEALTH

Solid phase peptide synthesis (SPPS) has become a standard approach for synthesis of peptides, especially in a laboratory setting. Heating the reactions in SPPS could significantly reduce the coupling and deprotection times. One of the heating methods is to use microwave which is becoming increasingly popular because it not only dramatically reduces the synthesis times, but also increases the crude peptide purity [1]. However, microwave peptide synthesizers are relatively expensive. In this study, we investigated whether SPPS using conduction heating can achieve similar result as microwave irradiation. CSBIO II and CEM Liberty Blue were used as heating resource of conduction and microwave heating, respectively. Four peptides with length of 18mer, 19mer, 20mer (Bivalirudin) and 39mer (Exenatide) were selected as examples. The peptides were synthesized using the same synthesis protocol at 90 °C including identical coupling, deprotection and washing cycles. The differences between the two approaches are the temperature of washing DMF (90 °C vs 23 °C for conduction and microwave heating, respectively) and overall synthesis cycle time (17 min vs 13 min in conduction and microwave heating, respectively). Both conduction and microwave heating generated comparable results with crude purity of 52.0% vs 51.7%, 49.0% vs 57.3%, 62.8% vs 57.1%, 37.0% vs 30.5% for 18mer, 19mer, 20mer and 39mer, respectively. One of the advantages of conduction heating is the uniformly and consistently delivered temperature during the synthesis which could minimize racemization and side reactions caused by spikes and hotspots typically associated with microwave heating. In addition, conduction heating is also a more cost-efficient heating method when compared to expensive microwave heating technology.

SCHOOL OF

MEDICINE

Methods Materials and general methods

Solid phase peptide synthesis

The peptides were synthesized on Rink amide resin (loading 0.43 mmol/g) using Oxyma/DIC coupling method on 0.1 mmol scale. The same resin and amino acid lots were used for all synthesis. Fmoc deprotection was achieved with 20% 4-methyl piperidine. The peptides were cleaved off the beads at room temperature for 3 hours with a cocktail containing trifluoroacetic acid (TFA), 5% phenol, 5% water, 5% thioanisole and 2.5% triisopropylsilane. Instruments used for peptide synthesis



CEM Liberty Blue



CSBIO II

Selected peptides for the study

Four different peptides (18mer, 19mer, 20mer and 39mer) were used for the evaluation.



HPLC was done in Shimadzu LC2030-C. Solution A: water with 0.1% TFA; Solution B: acetonitrile with 0.1% TFA. Flow rate: 1.0 mL/min, UV detection: 214 nm.

Comparison of Microwave and Conduction Heating for Solid Phase Peptide Synthesis

Ruiwu Liu, Yousif Ajena, Lucas N. Solano, and Kit S. Lam

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^ Soluti	on contains 0.5	VI DIC (1.0 n	IL), 1.0 M O	Amino	196.00	8
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Peptide	e synt	hesis	protoc	cols				HPLC Profiles of peptides
Standard	protoco	ls in mic	rowave a	and cond	duction heating	ng		18mer from CEM microwave
0.10	0 mmol CEM Sta	ndard Single Cou	pling	0.1	10 mmol CSBIO II Standar	rd Single Coupling	1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1	mAU IE PDA Multi 2 214nm, 4nm
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2	Wash		2		2 Deprotection @	3 min 6		
	Wash		3		4 Wash	5		
5	Coupling @	2 min	4*	1000	5 Wash	5	1000	
Total t	time: 5 min. Ter	mperature: 90°C		A	7 Wash	5	A	
* Solution	contains 0.5 M	1 DIC (1.0 mL), 1	1.0 M oxyma		8 Wash	5		min Peak Table> PDA Ch2 214nm
(U. 5 mL) a acid to bea	and U.2 M Fmo ads: 5 eq	c-amino acid (2.	5 mL). Amino	1	Coupling @ 30) min 4* 5		Ret. Time Height Height% Area Area% 9.692 19155 0.836 375262 1.278 10.657 14647 0.639 158644 0.540
				1	11 Wash	5		10.892 30393 1.326 569901 1.940 11.278 192028 8.378 2975733 10.131 11.751 1279098 55.806 15423572 52.510 10.901 55.806 56250 50.901
Madified	o qui vol	ant proto		Tot	Wash	5		12.049 12/2/0 5.553 9/5358 3.321 12.278 83051 3.623 953151 3.245 12.606 117032 5.106 2018122 6.871 12.973 10240 5.246 1728075 5.876
woattiea	equival	ent proto	0001	101	ai ume. 47 min. Temp			12.573 120240 5.246 172075 5.876 13.156 113779 4.964 1280743 4.360 13.389 137673 6.007 1715966 5.842 13.812 57665 2.516 1200052 4.086
0.10 mm	ol Modified Sing	le Coupling			Temperature	Time per Note		2292031 100.000 29372580 100.000
Cycle	Step	Volume (mL)	- 10	90 °	C throughout the entire	CSBio synthesizer	er has a	19mer from CEM microwave
2 Depro	Wash	5		synth	nesis protocol. 90 °C for	heating block that	hat can	<chromatogram></chromatogram>
3	Wash	5	Conductio	on heating both Bio II) well	the reaction vessel, as	17 min maintain h throughout synthe	heating besis as	mAU PDA Multi 2 214nm,4nm
4 5	Wash Wash	5		(pre-s	solvent delivery of the	well as a heating	ng block	
6	Wash	5	-98	depro	otection and wash solvent)	for pre-solvent del	elivery othesizer	1000-
8 Cou	vvasn Ipling @ 5 min	5 4*	- 25	90 °C	C only during deprotection	system only	allows	
9	Wash	5	Microway	ive (CEM) and c	coupling	10 min microwave	during	
10 T	Wash	5				coupling steps	anu	
	remperature. 90		* Delia	town and two of		the CCDie eventheseizer th	44.0	2.5 5.0 7.5 10.0 12.5 15.0 17.5 min
			[~] Delly	very and transfe	er speeds are slower in an and the wash st	n the CSBIO synthesizer, tr	tne	PDA Ch2 214nm Ret. Time Height Height Height% Area
					ingoly daming the wall of	000		9.816 43327 1.679 799075 2.325 10.593 30652 1.188 590913 1.719 10.916 269640 10 450 2838175 8 259
							and the second second	11.097 100089 3.879 1195480 3.479 11.437 135443 5.249 2030384 5.908 11.836 1610449 62 417 19525709 56 816
10.0 L 10.0								12.368 107165 4.153 1806171 5.256 12.770 56515 2.190 939128 2.733 13.166 61597 2.387 1074779 3.127
								13.552 117274 4.545 2895702 8.426 14.033 33932 1.315 525073 1.528 2580162 100.000 34366363 100.000
Resi	ilts						100 million (1997)	
11000	AILO							20mer from CEM microwave
Composi			with a fun	antidaa	mede with m	ieroweve in C		<chromatogram></chromatogram>
Comparis	son of c	ruae pu	rity of po	eptides	made with m	licrowave in C		mAU 1000
and cond	duction h	neating in	n CSBIO	II using	a standard p	rotocol (baselii	ine)	
							100 100 100	
	Peptide II	CSBio II	14h 16m	1140 mL	52.1%			
	18mer	CEM	1h 35m	351 mL	36.0%			
	19mer	CEM	150 3m 1h 40m	366 mL	25.6%			9.631 13.23 13.23 16.856
	20mer	CSBio II	15h 50m	1262 mL	59.8%			2.5 5.0 7.5 10.0 12.5 15.0 17.5
		CEM CSBio II	1h 48m 30h 43m	392 mL 2421 mL	47.4% 32.6%		100 100	<peak table=""></peak>
	39mer	CEM	4h 16m	714 mL	A big and broad			PDA Ch2 214nm Ret. Time Height Height% Area Area% 9.631 29997 2.028 489485 2.582
					peak*			3.031 23337 2.020 403403 2.302 11.304 12668 0.856 437189 2.306 11.787 39884 2.696 584509 3.084 10.402 4040000 70000 3.084
	* This is prob	ably because t	he delivered vo	olume of coup	ling, deprotection and		1. 19 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	12.188 1050209 70.996 11920204 62.885 12.507 78578 5.312 704921 3.719 12.747 153907 10.404 2277929 12.017
v	washing solutio	ns was not end	ough to allow e	efficient mixing	with all beads due to			13.232 40598 2.744 861416 4.544 13.698 23562 1.593 358362 1.891 14.100 25464 1.721 616733 3.254
ir ir	ncreased volum	ne of beads, res	ulting in incompl	lete reactions.			1000	14.190 23484 1.721 616733 3.234 14.561 9376 0.634 487285 2.571 16.856 15013 1.015 217594 1.148
	1000							
				1:			300	
Comparis	on of cr	ude puri	ty of pep	tides ma	ade with micr	owave in CEM	anu	39mer from CEM microwave
Comparis conductio	on of cr on heatir	ng in CSE	ty of pep BIO II usi	otides ma ing an ec	ade with micr quivalent and	owave in CEM optimized pro	otocol	39mer from CEM microwave
Comparis conductio	on of cr on heatir	ng in CSE	ty of pep 3IO II usi	otides ma ing an ec	ade with micr quivalent and	owave in CEM optimized pro	otocol	39mer from CEM microwave
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protocol that is capable to synthesize long Both conduction and microwave heating gave irity as seen in the case of four peptides, when

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istry and Chemical Biology Shared Resource (CCCBSR) tilization of the CCCBSR was supported by the UC Davis the National Cancer Institute (P30CA093373).

ored the research and presentation.