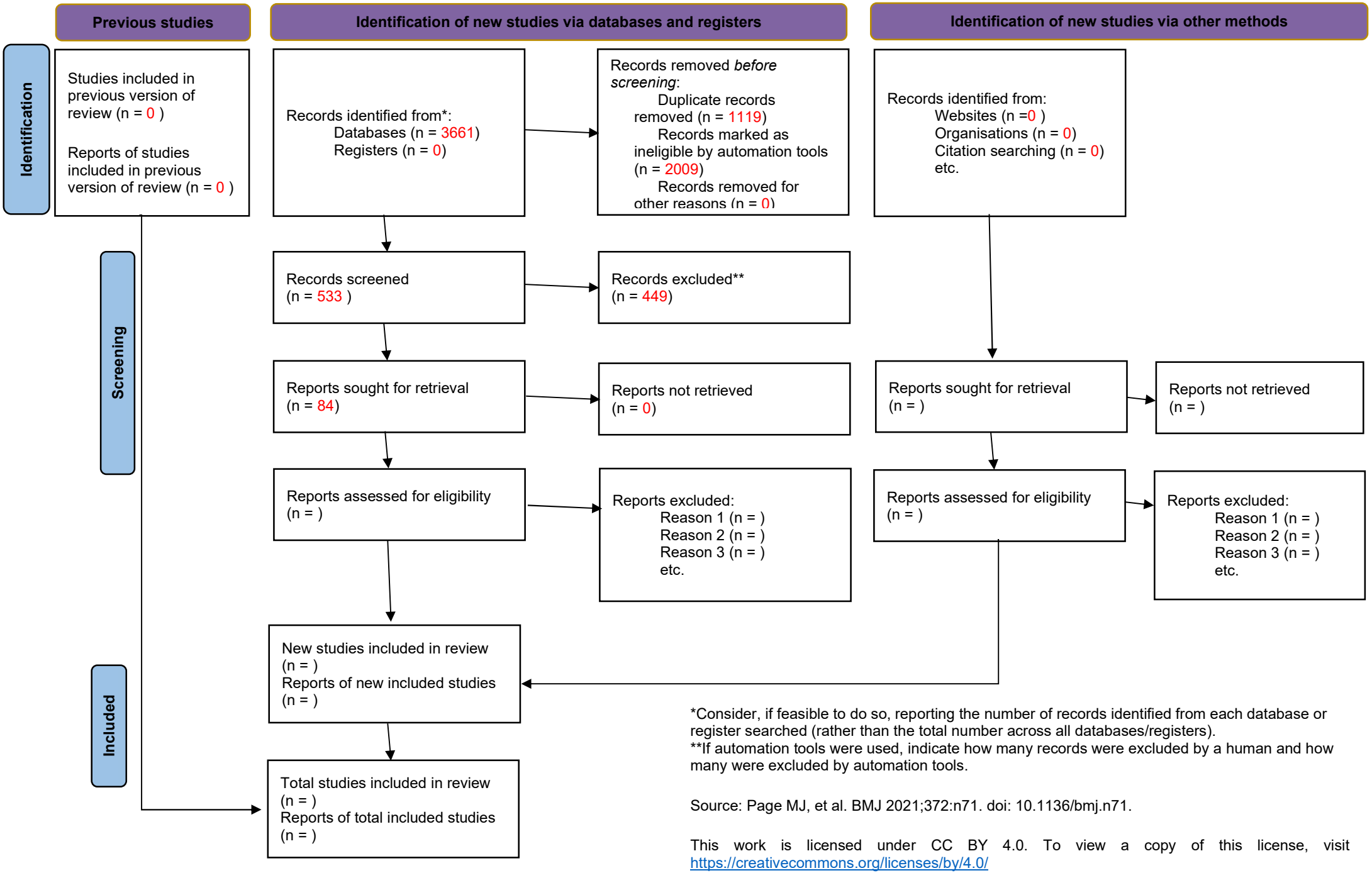
Supplementary Information

Microfluidics for Drug Encapsulation and Controlled Release: A Systematic Review of Recent Advances

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Figure S1. PRISMA 2020 flow diagram for updated systematic reviews which included searches of databases, registers and other sources



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

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Table S1. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page: Microfluidics for Drug Encapsulation and Controlled Release: A Systematic Review of Recent Advances
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Structured abstract, page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	“Introduction, Section 1 (‘The Need for Drug Encapsulation’)
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	“Introduction, final paragraph (statement that the work ‘systematically focuses on microfluidic-assisted encapsulation and controlled release of therapeutic cargos between 2020–2025’).
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods, Section 2.1 (‘Eligibility criteria’).
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods, Section 2.2 ‘Information sources and search strategy’, paragraph 1 PubMed, Scopus, Web of Science
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Methods, Section 2.2, paragraphs 2–3: core search string and carrier-specific secondary searches; Supplementary Table S1 (full database-specific strategies)
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods, Section 2.3 (‘Selection process and data collection’), paragraphs describing automated pre-filter, dual independent screening of 533 records, and consensus resolution; Supplementary Figure S1 (PRISMA flow diagram)
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods, Section 2.3, final paragraph (standardized extraction form and variables collected)
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods, Section 2.1 (outcomes specified as particle size/size distribution, PDI, encapsulation efficiency/drug loading, and release profiles) and Section 2.3 (data extraction fields)
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Methods, Section 2.3 (device material, configuration and mixing principle, carrier type, cargo type, flow-rate ratio, total flow-rate, mixing geometry, comparative advantages/limitations vs bulk methods)

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Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Not applicable – no formal risk-of-bias tool was applied because no meta-analysis or pooled effect estimates were performed (narrative synthesis of technological outcomes only)
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Not applicable – no pooled effect measures (e.g., risk ratios, mean differences) were calculated; results are reported as descriptive statistics (EE, PDI, size, release profiles) within individual studies
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Methods, Section 2.1 (carrier types eligible) and Section 3.3 (subsections a–c: microspheres, nanoparticles, hydrogels, liposomes/LNPs), where studies are grouped by carrier class and microfluidic paradigm.
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Methods, Section 2.3 (standardization of extracted variables and grouping of comparable outcomes such as size, PDI, and encapsulation efficiency). No imputation or data conversion beyond unit harmonization was performed
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Results, Section 3.3 (Tables 2–4 and schematic Figures for microfluidic architectures, flow-focusing strategies and hydrogel microgels)
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Results, Section 3.3 and Discussion: narrative synthesis structured by carrier class (microspheres, PNPs, hydrogels, liposomes/LNPs) and by microfluidic strategy (nanoprecipitation, droplet-based, core–shell architectures). No statistical meta-analysis was performed
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not applicable – between-study heterogeneity was not quantified formally; instead, differences in device materials, mixing geometries and formulation parameters are discussed qualitatively in Section 3.3 and the Discussion
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable – no quantitative syntheses or sensitivity analyses were performed
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applicable – no formal assessment of reporting bias was conducted; potential publication and selection biases are discussed qualitatively in the Discussion (limitations of the evidence).
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applicable – no formal GRADE-type certainty assessment was undertaken
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Methods, Section 2.3 (numbers 2,542 → 533 → 84) and Supplementary Figure S1 (PRISMA 2020

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			flow diagram)
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Not explicitly tabulated; reasons for exclusion are described in general terms in Methods, Section 2.1–2.3 (e.g., diagnostic-only microfluidics, device-fabrication without encapsulation data, reviews/editorials). No separate list of excluded full-text reports is provided
Study characteristics	17	Cite each included study and present its characteristics.	Results, Section 3.3 (carrier-specific subsections) and Tables 2–4, where for each included study device material, microfluidic configuration, carrier type, cargo and key outcomes are summarized
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Not applicable – no formal risk-of-bias assessment was carried out
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Results, Section 3.3 (e.g., paragraphs describing Aboelela et al. for PLGA PNPs, He et al. for 5-FU chitosan microspheres, Dou et al. for leuprolide core–shell PLGA, López Cerdá et al. for hybrid LPNs) and corresponding tables.
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Not applicable – no statistical syntheses or meta-analyses were conducted; see narrative comparison in Section 3.3 and Discussion
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applicable – no statistical syntheses or meta-analyses were conducted; see narrative comparison in Section 3.3 and Discussion.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable – no statistical syntheses or meta-analyses were conducted; see narrative comparison in Section 3.3 and Discussion.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable – no statistical syntheses or meta-analyses were conducted; see narrative comparison in Section 3.3 and Discussion.
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable – no formal reporting-bias analysis; potential biases discussed qualitatively in Discussion (limitations)
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not applicable – certainty not graded formally
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion, first 2–3 paragraphs (overall interpretation of microfluidic advantages over bulk methods in terms of monodispersity, EE, and control of protein corona)
	23b	Discuss any limitations of the evidence included in the review.	Discussion, paragraph(s) on limitations of the included studies (small sample sizes, lack of in

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			vivo data, limited head-to-head comparisons vs bulk methods).
	23c	Discuss any limitations of the review processes used.	Discussion, paragraph noting the restriction to 2020–2025, English/Spanish language, database choice (PubMed, Scopus, Web of Science) and absence of trial registries or gray literature searches
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion, final paragraphs (implications for translation to GMP, personalized medicine, and future microfluidic device design)
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods, Section 2.2 (explicit statement that the protocol was not prospectively registered and that no separate protocol is available)
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods, Section 2.2 (explicit statement that the protocol was not prospectively registered and that no separate protocol is available)
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Methods, Section 2.2 (explicit statement that the protocol was not prospectively registered and that no separate protocol is available)
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Acknowledgments/Funding section (sources of financial or non-financial support, if present; otherwise state 'no specific funding')
Competing interests	26	Declare any competing interests of review authors.	Conflict of interest statement at the end of the manuscript
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Not applicable – the review did not generate a new quantitative dataset; extracted data are available from the corresponding author on reasonable request

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.
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