



NOVEL DRUG DELIVERY SYSTEM

Dr. Vivek S. Tarate
Ms. Rajashri E. Badadare-Jadhav
Ms. Sonal C. Gaikwad
Ms. Ashwini U. Nalawade
Mr. Akshay V. Bhenki

Kripa Drishti Publications, Pune.

NOVEL DRUG DELIVERY SYSTEM

Dr. Vivek S. Tarate

Vice-Principal & Professor SDNCRES's,
Late Narayandas Bhawandas Chhabada Institute of Pharmacy,
Raigaon, Satara.

Ms. Rajashri E. Badadare-Jadhav

HOD, MSS's College of Pharmacy, Medha.

Ms. Sonal C. Gaikwad

Assistant Professor, MSS's College of Pharmacy, Medha.

Ms. Ashwini U. Nalawade

Assistant Professor, MSS's College of Pharmacy, Medha.

Mr. Akshay V. Bhenki

Assistant Professor,
Shri Ganpati Institute of Pharmaceutical Sciences and Research,
Tembhurni.

Kripa-Drishti Publications, Pune.

Book Title: **Novel Drug Delivery System**

Authored By: **Dr. Vivek S. Tarate, Ms. Rajashri E. Badadare-Jadhav
Ms. Sonal C. Gaikwad, Ms. Ashwini U. Nalawade
Mr. Akshay V. Bhenki**

Price: ₹675

1st Edition

ISBN: **978-81-976840-6-7**



Published: **July 2024**

Publisher:



Kripa-Drishti Publications

A/ 503, Poorva Height, SNO 148/1A/1/1A,
Sus Road, Pashan- 411021, Pune, Maharashtra, India.

Mob: +91-8007068686

Email: editor@kdpublications.in

Web: <https://www.kdpublications.in>

© Copyright Dr. Vivek S. Tarate Ms. Rajashri E. Badadare-Jadhav, Ms. Sonal C. Gaikwad,
Ms. Ashwini U. Nalawade , Mr. Akshay V. Bhenki

All Rights Reserved. No part of this publication can be stored in any retrieval system or reproduced in any form or by any means without the prior written permission of the publisher. Any person who does any unauthorized act in relation to this publication may be liable to criminal prosecution and civil claims for damages. [The responsibility for the facts stated, conclusions reached, etc., is entirely that of the author. The publisher is not responsible for them, whatsoever.]

PREFACE

A novel approach known as the "**Novel Drug Delivery System**" makes use of cutting-edge concepts, technologies, and techniques to deliver active molecules at a safe concentration that will nonetheless have the desired pharmacological effect. To achieve the desired effect for a longer period of time, the novel drug delivery system can also maintain the plasma drug concentration in a controlled manner.

In order to deliver the contained medication to the target tissues in a preprogrammed way, carrier modules have been developed using interdisciplinary approaches and state-of-the-art technology. The location of drug targeting changes drug by activity and kinetics, among other challenges associated with the novel drug delivery system. Each patient has a unique metabolism, and each drug may react differently in terms of efficiency, which makes it challenging to define. Clinical trials are costly and challenging to carry out.

This book's objective is to compile an overview of significant, targeted technologies utilised in drug delivery systems (DDS). This selection takes significant medications, novel technologies like nanoparticles, and significant therapeutic applications into account. For pharmacologists and pharmaceutical scientists employed in both industry and academia, this book will be a valuable resource. For scientists and physicians working in various fields related to the development of DDS, including chemical engineering, protein engineering, gene therapy, and so forth, it contains pertinent information. Executives overseeing research and development at several hundred companies creating drug delivery technologies will find this to be a valuable resource. For undergraduate and graduate students, as well as anybody interested in the operation and performance of drug delivery systems, this is an invaluable textbook and resource.

Objectives:

Upon Completion of the Course student shall be able

1. To understand various approaches for development of novel drug delivery systems.
2. To understand the criteria for selection of drugs and polymers for the development of Novel drug delivery systems, their formulation and evaluation.

Abbreviations

Active Pharmaceutical Ingredient (API)
Apparent partition coefficient (APC)
Autosomal Dominant Retinitis Pigmentosa (ADRP)
Blood-Retina Barrier (BRB)
Bruch's Membrane (BM)
Chronic Obstructive Pulmonary Disease (COPD)
Ciliary Neurotrophic Factor (CNTF)
Clearance (CL)
Complementarity-Determining Regions (CDRs)
Controlled Release (CR)
Critical Packing Parameter (CPP)
Cryo-Transmission Electron Microscopy (cryo-TEM)
Cytomegalovirus (CMV)
Dehydration and Rehydration (DRV)
Development of Intrauterine Device (IUD)
Diazo-Oxo-Norleucine (DON)
Dicetyl Phosphate (DCP)
Di-O-Octadecenyl-3-Trimethylammonium Propane (DOTMA)
Distearoyl-Sn-Glycero-Phosphatidylcholine (DSPC)
Dose (D)
Drug Delivery Systems (DDS)
Dry Powder Inhalers (DPIs)
Effective Dose (ED)
Encapsulated Cell Technology (ECT)
Enhanced Permeability and Retention (EPR)
Entrapment Efficiency (EE)
Ethylene Vinyl Acetate (EVA)
Extrusion Technique (VET)
Floating Drug Delivery Systems (FDDS)
Fluocinolone Acetonide (FA)
Freeze And Thaw (FAT)
Gastric Retention Time (GRT)
Glutamic Acid (GA)
Glyceraldehyde-3-Phosphate Dehydrogenase (GAPDH)
High-Pressure Homogenization (HPH)
Human Immunodeficiency Virus (HIV)
Human Papillomavirus (HPV)
Hydrodynamic Radius (Rh)
Hydrodynamically Balanced System (HBS)
Hydrophilic-Lipophilic Balance (HLB)
Hydroxypropyl Cellulose (HEC)
Hydroxypropyl Cellulose (HPC)

Hydroxypropyl Methylcellulose (HPMC)
Hypoxanthine Aminopetrin Thymidine (HAT)
Hypoxanthine-Guanine-Phosphoribosyl Transferase (HGPRT)
Implantable Drug Delivery Systems (IDDSs)
include hydroxypropyl methylcellulose (HPMC)
Inflammatory Bowel Disease (IBD)
Internal Limiting Membrane (ILM)
Irritable Bowel Syndrome (IBS)
Large Unilamellar Liposomes/Vesicles (LUV)
Large Unilamellar Vesicles (LUVs)
Lethal Dosage (LD)
Lipid Drug Conjugate (LDC)
Lipopolysaccharide (LPS)
Lipoteichoic Acid (LTA)
Loaded Folic Acid (FA)
Low Density Lipoprotein (LDL)
Lower Critical Solution Temperature (LCST)
Magnetic Nanoparticles (MNPS)
Magnetic Resonance Imaging (MRI)
Matrix Metalloproteinases (MMPs)
Maximum Therapeutic Concentration (MTC)
Medium Unilamellar Vesicles (MUL)
Metered-Dose Inhaler (MDI)
Metered-Dose Inhalers (MDIs)
Microneedles (MLs)
Minimum Effective Concentration (MEC)
Multilamellar Liposomes/Vesicles (MLV)
Multilamellar Vesicles (MLVs)
Multivesicular Liposomes/Vesicles (MVV)
Mycobacterial Membrane Protein Large5 (MmpL5)
Nanoparticles (NP)
Nanostructured Lipid Carriers (NLC)
Ocular Drug Delivery System (ODDS)
Ocular Therapeutic System (OTS)
Oligodeoxynucleotide (ODN)
Oligolamellar Vesicles (OLV)
Particle Replication in Non-Etting Templates (PRINT)
Phase change material (PCM)
Phosphotungstic Acid (PTA)
Poly (D, L-Glycolide) (PLG)
Poly (lactic acid) (PLA)
Poly 2-Hydroxyethyl Methacrylate (pHEMA)
Poly Acrylic Acid (PAA)
Poly Amidoamine (PAMAM)
Poly Cyanoacrylate (PCA)
Poly Ethylene Glycol (PEG)

Poly Lactic-Co-Glycolic Acid (PLGA)
Polyaprolctone (PCL)
Polydispersity Index (PDI)
Polyethylene Glycol (PEG)
Polyglycolic Acid (PGA)
Polyhydroxy Butyrate Vel (PHBV)
Polymeric Micelles (PMS)
Polyn-Isopropylacrylamide (PNIPAAm)
Polypyrrole (PPy)
Polyvinyl Alcohol (PVA)
Polyvinyl Chloride (PVC)
Polyvinylpyrrolidone (PVP)
Quantum Dots (QD)
Reticuloendothelial System (RES)
Retinal Pigment Epithelium (RPE)
Reverse Phase Evaporation (REV)
Rheumatoid Arthritis (RA)
Small Unilamellar Liposomes/Vesicles (SUV)
Small Unilamellar Vesicles (SUVs)
Sodium Carboxymethyl Cellulose (NaCMC)
Solid Lipid Nanoparticles (SLN)
Soluble Ophthalmic Drug Insert (SODI)
Stearyl Amine (SA)
Stratum Granulosum (SC)
Toll-Like Receptor (TLR)
Transdermal Drug Delivery Systems (TDDS)
Triamcinolone Acetonide (TA)
Tumor Necrotic Factor-alpha (TNF-alpha)
Ultraviolet Radiation (UV)
Unilamellar Vesicles (ULV)
Upper Gastrointestinal Tract (GIT)
Vascular Endothelial (VE)
Vascular Permeability Enhancement (VPE)

INDEX

Unit 1	1
1.1 Introduction:.....	1
1.1.1 Terminology/Definitions:.....	4
1.1.2 Rationale of Controlled Drug Delivery:.....	5
1.1.3 General Advantages:	6
1.1.4 Disadvantages of the controlled drug delivery systems Various disadvantages of the controlled drug delivery systems are mentioned below:	8
1.1.5 Selection of Drug Candidates:	9
1.1.6 Approaches to Design Controlled-release Formulations:	20
1.1.7 Ion Exchange Principles:.....	26
1.1.8 Physicochemical Properties of Drugs Suitable for Controlled Release Formulations:	29
1.2 Polymers:	35
1.2.1 Introduction:	35
1.2.2 Classification of Polymers:.....	35
1.2.3 Structure of Polymers:.....	37
1.2.4 Properties of Polymers:	38
1.2.5 Various Polymers Used in Drug Delivery:.....	41
1.2.6 Advantages:	48
1.2.7 Difficulties and Challenges:	50
1.2.8 Drug Delivery Devices-Requirements of Polymers in Drug Delivery System:.....	51
1.2.9 Application Scopes of Polymers in Drug Delivery System:	56
1.2.10 Polymers Used in The Formulation of Controlled Release Drug Delivery Systems:.....	59
Unit 2	61
2.1 Microencapsulation: Definition:	61
2.1.1. Advantages And Disadvantages of Microencapsulation:.....	64
2.1.2 Microspheres/Microcapsules:	67
2.1.3 Microparticles:	73
2.1.4 Method of Microencapsulation:.....	74
2.1.5 Application:	76
2.2 Mucosal Drug Delivery System: Introduction:	77
2.2.1 Principles of Bioadhesion/Mucoadhesion:	79
2.2.2 Concepts:	81
2.2.3 Advantages and Disadvantages:	83

2.2.4 Transmucosal Permeability and Formulation Considerations of Buccal System:.....	84
2.3 Implantable Drug Delivery System: Introduction:	86
2.3.1 Advantages and Disadvantages:	88
2.3.2 Concept of Implants and Osmotic Pump:.....	89
Unit 3.....	92
3.1 Transdermal Drug Delivery Systems: Introduction:	92
3.1.1 Permeation Through Skin:.....	92
3.1.2 Factors Affecting Permeation:.....	95
3.1.3 Permeation Enhance:.....	97
3.1.4 Basic Components of TDDS:	98
3.1.5 Formulation Approaches Of TDDS:	99
3.2 Gastro-Retentive Drug Delivery Systems:.....	103
3.2.1 Advantages of GRDDS:	104
3.2.2 Disadvantages of GRDDS:.....	104
3.2.3 Approaches For GRDDS:.....	104
3.2.4 Inflatable Gastrointestinal Delivery Systems:	108
3.2.5 Application of GRDDS:	109
3.3 Nas Pulmonary Drug Delivery System:.....	110
3.3.1 Introduction to Nasal Routes of Drug Delivery:.....	110
3.3.2 Formulation of Inhalers:	112
3.3.3 Nasal Sprays:	115
3.3.4 Nebulizers:.....	115
Unit 4.....	117
4.1 Targeted Drug Delivery:	117
4.2 Introduction LIPOSOMES:.....	127
4.2.1 Liposomes and Their Structural Composition:.....	130
4.2.2 Properties of Liposomes:	132
4.2.3 Advantages and Disadvantages of Liposomes:	132
4.2.4 Applications of Liposomes:.....	133
4.2.5 Classification of Liposomes	136
4.3 Niosomes:.....	145
4.3.1 Structure of Niosomes:	145
4.3.2 Composition of Niosomes:	148
4.3.3 Classification and Formulation Techniques of Niosomes.....	151
4.4 Nanoparticles:.....	156
4.4.1 Mechanism of Drug Delivery via Nanoparticle:.....	158
4.4.2 Types of Nanoparticles:.....	159
4.4.3 Preparation of Nanoparticles:.....	167
4.5 Monoclonal Antibodies and Their Applications:	169
4.5.1 Types of Monoclonal Antibodies:.....	170
4.5.2 Production of Monoclonal Antibodies:	172

4.5.3 Functions and Applications of Monoclonal Antibodies:.....	173
Unit 5	175
5.1 Ocular Drug Delivery System: Introduction:.....	175
5.1.1 Intra Ocular Barriers:	177
5.1.2 Methods to Overcome Barriers:.....	181
5.1.3 Ocular Formulations:	184
5.2 Intrauterine Drug Delivery Systems:.....	200
5.2.1 Development of Intrauterine Device (IUD):	204
5.2.3 Applications:.....	206
References.....	209

List of Figures

	Figures Name	Page No.
Figure 1.1:	Classification of Modified Release Dosage Form.	21
Figure 1.2:	Schematic Diagram of The Drug Release from the Reservoir System by Dissolution of Polymeric Matrix	24
Figure 1.3:	Schematic representation of an erosion-controlled system	25
Figure 1.4:	Types of Polymers	37
Figure 1.5:	Diffusion based drug delivery system.	41
Figure 1.6:	Hydrogel based drug delivery system.	42
Figure 1.7:	Various drug release mechanisms.	42
Figure 1.8:	PGA (poly glycolic acid)	42
Figure 1.9:	PGA (poly glycolic acid)	43
Figure 1.10:	Poly-l-glutamic acid	43
Figure 1.11:	Poly lactic acid	44
Figure 1.12:	PNIPA Am [Poly(N-isopropylacrylamide)]	44
Figure 1.13:	pHEMA [Poly 2-hydroxyethyl methacrylate]	45
Figure 1.14:	PPy [Polypyrrole]	45
Figure 1.15:	PAMAM [Poly (amidoamine)]	46
Figure 1.16:	DEXTRAN	46
Figure 1.17:	Adsorption to the surface (ionic contact), direct covalent conjugation with functional groups on the surface, and encapsulation within hydrophobic cavities inside branching clefts—all allow for the simultaneous delivery of hydrophilic and hydrophobic medicines.	52
Figure 1.18:	Microsphere and microcapsule	53
Figure 1.19:	Hydrogel.	54
Figure 2.1:	Flowchart of Microencapsulation in Novel drug delivery system	61
Figure 2.2:	Microencapsulation Coating	63
Figure 2.3:	Sub-Points of Advantages of Microencapsulation	66
Figure 2.4:	Sub-Points of Disadvantages of Microencapsulation	67
Figure 2.5:	Microspheres Are Spherical Microparticles with Specific Dimensions Between 1um and 1000um.	68
Figure 2.6:	Fabrication And Application of Complex Microcapsule and Microsphere	72
Figure 3.1:	Anatomy of Skin	92
Figure 3.2:	Routes of Skin Penetration	94

	Figures Name	Page No.
Figure 3.3:	Membrane Permeation-Controlled System	100
Figure 3.4:	Matrix Diffusion Controlled TDD System	101
Figure 3.5:	Adhesive Dispersion – Type Systems	101
Figure 3.6:	Micro Reservoir Dissolution Controlled TDD System	102
Figure 3.7:	Mechanism of Floating Systems	105
Figure 3.8:	Microballoons	107
Figure 3.9:	High-Density Systems	108
Figure 3.10:	Inflation Chamber	108
Figure 3.11:	Mechanism of Drug Absorption in Nasal Drug Delivery	111
Figure 3.12:	Dry Powder Inhalers	113
Figure 3.13 (a):	Jet Nebulizer	115
Figure 3.13 (b):	Ultrasonic Nebulizer	115
Figure 3.14:	Mesh Nebulizer	116
Figure 4.1:	Schematic representation of (A) ligand receptor-mediated interaction, (B) radiotherapy, and (C) photothermal therapy.	118
Figure 4.2:	Advantages offered by targeted drug delivery compared with conventional dosage forms.	119
Figure 4.3:	Different reason or need for Drug targeting	123
Figure 4.4:	Types of Targeted Drug Delivery System	125
Figure 4.5:	Types of Targeted Drug Delivery System (Passive & Active Targeting)	125
Figure 4.6:	Liposome	128
Figure 4.7:	An illustration of liposome and its structural components.	130
Figure 4.8:	An illustration of the preparation of liposomes and cholesterol roles in its stability.	131
Figure 4.9:	An illustration of different application areas of liposomes: photodynamic therapy, drug delivery, disease diagnosis, and vaccine therapy.	135
Figure 4.10:	An illustration of unilamellar and multilamellar vesicular structures.	137
Figure 4.11:	Multilamellar Liposomes/Vesicles (MLV)	138
Figure 4.12:	An illustration of different types of liposomes based on their composition and targeting strategies	140
Figure 4.13:	Method of Liposomes Preparation	141
Figure 4.14:	Schematic representation of Niosomes	146

	Figures Name	Page No.
Figure 4.15:	Schematic Representation of the Ether Injection Technique.	153
Figure 4.16:	Illustrative scheme for the formulation of niosomes with the micro-fluidization technique.	153
Figure 4.17:	Illustrative scheme for the formulation of niosomes with the multiple membrane extrusion technique.	154
Figure 4.18:	Schematic representation of the ether injection technique.	154
Figure 4.19:	Illustrative scheme for the formulation of niosomes with the lipid injection technique.	155
Figure 4.20:	Illustrative scheme for the formulation of niosomes with bubble technique.	155
Figure 4.21:	Illustrative scheme for the formulation of niosomes with reverse-phase evaporation technique.	156
Figure 4.22:	Mechanism of Drug Delivery via Nanoparticle	159
Figure 4.23:	Solid Lipid Nanoparticles	160
Figure 4.24:	Structure of Liposome	161
Figure 4.25:	Nanostructured lipid carriers	162
Figure 4.26:	Endohedral Aza fullerenes	163
Figure 4.27:	Nanoshells	164
Figure 4.28:	Quantum Dots with Coatings	165
Figure 4.29:	Super Paramagnetic Nanoparticle	166
Figure 4.30:	Production of Monoclonal Antibodies	172
Figure 5.1:	Anatomy of the Eye	177
Figure 5.2:	Lens	180
Figure 5.3:	Ocular Anodal Iontophoresis Delivery of Positively Charged	182
Figure 5.4:	Vitreous	183
Figure 5.5:	Eye-Drops	184
Figure 5.6:	Ophthalmic Inserts	185
Figure 5.7:	Diffusional insert or ocuserts	186
Figure 5.8:	Osmotic Inserts	186
Figure 5.9:	Contact Lens and Ocular Insert	188
Figure 5.10:	Punctual Plug	192
Figure 5.11:	The effectiveness of ocular hypotensive agents in eye drops in conjunction with punctual plug occlusion is documented	192
Figure 5.12:	Subconjunctival/Episcleral Implants	193
Figure 5.13:	Durasert™ Technology System	194

	Figures Name	Page No.
Figure 5.14:	Gene Therapy	196
Figure 5.15:	Scleral Plug Therapy	197
Figure 5.16:	Aptamer	199
Figure 5.17:	Vessels and Nerves	204

List of Tables

Table Name	Page No.
Table 1.1: Hixson-Crowell Model	18
Table 1.2: Marketed Formulations of Drugs with The Technology Used	21
Table 1.3: Physicochemical Properties of Drug	30
Table 2.1: Difference in bioadhesion/mucoadhesion	80
Table 2.2: Advantages and Disadvantages	83
Table 4.1: The extensive sizes range of liposomes are:	132
Table 4.2: Advantages and Disadvantages of Niosomes According to The Literature	147
Table 4.3: Types and Typical examples of Chemicals Used in Formulation of Niosomes.	149
Table 5.1: Components of Osmotic Inserts	187
Table 5.2: Ocular Inserts Devices	191
Table 5.3: Time of IUD insertion	208

ABOUT THE AUTHORS



Dr. Vivek S. Tarate is currently working as Vice-Principal & Professor at SDNCRES's, Late Narayandas Bhawandas Chhabada Institute Of Pharmacy, Raigaon, Satara. He has completed M.Pharm in Pharmaceutics from Savitribai Phule Pune University, Pune. He has completed PhD in Pharmaceutical Sciences, PhD in Naturopathy (Diabetes Reversal). He received another PhD (HC) in subject healthcare from Commonwealth University, kingdom of Tonga for his contribution to healthcare sector. He is also appointed as VIP member of International Teachers Association. He also Completed Certificate and Diploma courses in Naturopathy, Medical Astrology (International Medical Astrologer), Cupping Therapy (TCM – China), Code Blue Trainer (Lincoln University, Malaysia), Nutrition & Diet Planning (FAB Academy, USA) and Regulatory Affairs (IADL, UK approved) from various national & international Universities. He received 10 Indian Patent Grants (Designs), 1 Indian Utility Patent grant & 13 International Patent Grants out of which 1 from Australia, 4 from Germany, 4 from South Africa & 4 from UK countries. His research interest includes GRDDS, Nanoparticles, Herbal formulations, Type 1 & 2 diabetes reversal. He received 5 Copyrights grant from Copyright Office, Government of India for his value-added courses designs. He has published more than 10 books in Pharmacy field & his books are indexed in Worldcat Library and connected to worldwide libraries. He is reviewer & editor of so many journals & publication houses. He published review as well as research papers in various UGC Care, Scopus journals. He is a founder of Ssuvijayaa Group. He is a Global Outreach - Postdoctoral Member of the American Society for Microbiology. He is also working as consultant for Hospitals and Pharma giants. In 2021 he is appointed and upgraded as I.I Paramedic at Hospital & Institute of Integrated Medical Sciences, Chandigarh. He is Member of All India Council for Technical Skill Development. He is a fellow member of Screenwriters Association, Mumbai. He is a certified Psychological Counselor. He is also member of Indo-Vietnam medical board and appointed as Network of Influenza Care Expert. Recently for his contribution to Pharmacy Research & Development field he was felicitated by 49th Supreme Court's, Hon. Chief Justice of India, Justice Dr. Uday Lalit sir.



Ms. Rajashri E. Badadare-Jadhav is currently working as HOD at MSS's College of Pharmacy, Medha. She has completed M. Pharmacy in Pharmaceutics from YSPM'S YTC Satara. She has received one Indian Patent Grant (Design). Currently, she is pursuing PhD from Sandeep University Nashik. She has more than 7 years of experience in academics. She has published research and review papers in various journals.



Ms. Sonal C. Gaikwad is currently working as Assistant Professor at MSS's College of Pharmacy, Medha. She has completed M. Pharmacy in Pharmacology from YSPM'S YTC Satara. She has received one Indian Patent Grant (Design). She has more than 5 years of experience in academics. She has published research and review papers in various journals.



Ms. Ashwini U. Nalawade is currently working as Assistant Professor at MSS's College of Pharmacy, Medha. She has completed M. Pharmacy in Pharmacology from YSPM'S YTC Satara. She has received one Indian Patent Grant (Design). She has more than 5 years of experience in academics. She has published research and review papers in various journals.



Mr. Akshay V. Bhenki is currently working as an Assistant Professor in Shri Ganpati Institute of Pharmaceutical Sciences And Research, Tembhurni. He has 4 years of Experience in Academics. Also He is Pursuing his Ph.D in Sunrise University, Alwar, Rajasthan. His credential includes 3 Research Articles, 2 Review Articles in International Journals as well as 1 Book Publication He also received Two Indian Patent Grant (Design). He also Attended Various National and International Conferences on Various topics.



Kripa-Drishti Publications

A-503 Poorva Heights, Pashan-Sus Road, Near Sai Chowk,
Pune - 411021, Maharashtra, India.

Mob: +91 8007068686

Email: editor@kdpublications.in

Web: <https://www.kdpublications.in>

Price: ₹ 675

ISBN: 978-81-976840-6-7



9 788197 684067