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ORAL MICROSPHERES FOR THE MANAGEMENT OF THROMBOPHILIA

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ABSTRACT

Long-term antithrombotic medication is necessary to prevent major consequences including deep vein thrombosis and pulmonary embolism in people with thrombophilia, a disorder marked by a higher propensity for aberrant blood clot formation. Conventional oral anticoagulants sometimes have drawbacks such as fluctuating plasma drug levels, frequent dosing, gastrointestinal discomfort, and variable absorption. Drug delivery systems based on oral microspheres have shown promise in addressing these issues. Microspheres provide greater absorption, better medication stability in the gastrointestinal tract, controlled and prolonged drug release, and the possibility of targeted delivery. Recent developments in polymeric and lipid-based oral microspheres for thrombophilia treatment are compiled in this review, with particular attention paid to formulation techniques, material selection, drug loading tactics, and release mechanisms. Important in-vitro and in-vivo discoveries, present constraints, and potential future clinical translation opportunities are also highlighted. All things considered, oral microspheres are an innovative platform that holds great promise for enhancing treatment results and patient adherence in the treatment of thrombophilia.

Keywords: Oral microspheres, Thrombophilia,Antithrombotic therapy, Microencapsulation, Bioavailability, Sustained release.

Introduction:

A hematological condition called thrombophilia is defined by an increased propensity for blood clot formation as a result of anomalies in the coagulation system. It can be acquired, inherited, or the consequence of a mix of environmental and genetic factors. Venous or arterial thrombi can result from the disruption of the delicate balance between procoagulant and anticoagulant pathways. Deep vein thrombosis (DVT), pulmonary embolism (PE), and, in extreme situations, repeated pregnancy loss are common clinical symptoms.

Mutations like Factor V Leiden, prothrombin gene mutations, or deficits in natural anticoagulants such protein C, protein S, and antithrombin are frequently associated with inherited thrombophilia. Conversely, antiphospholipid syndrome, cancer, extended immobilisation, and the use of specific drugs are often linked to acquired thrombophilia.

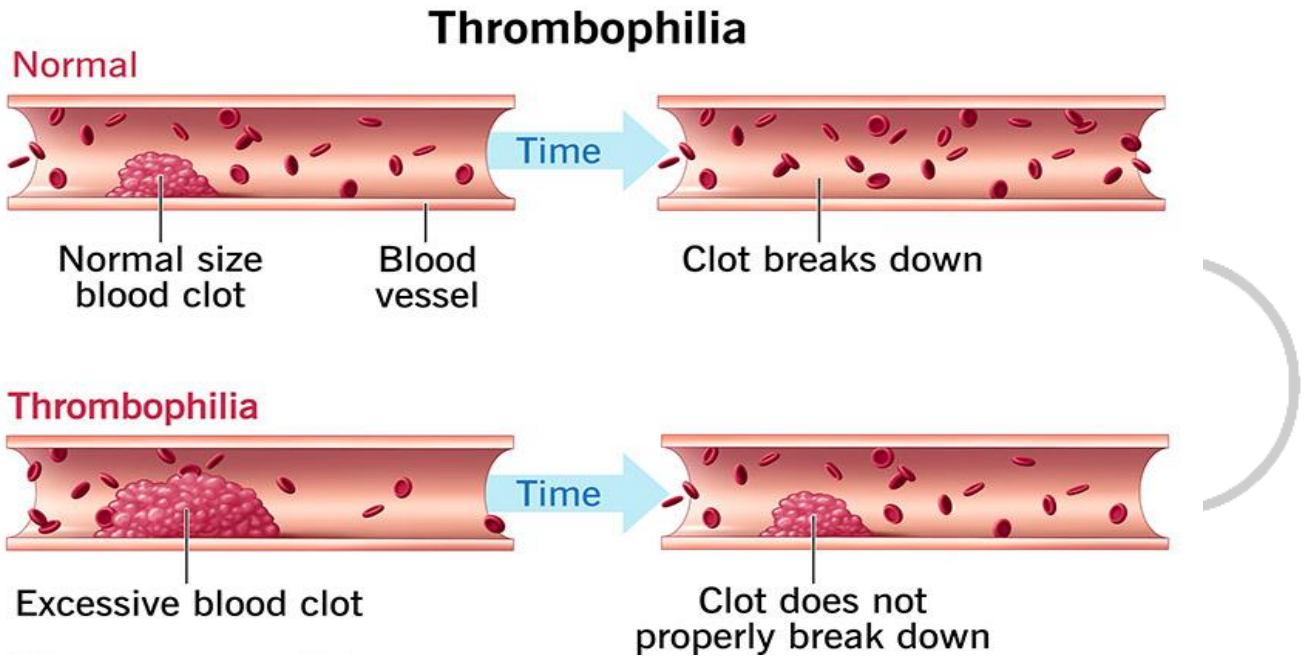

Fig 1:Schematic representation of blood clotting mechanism

Treatment of Thrombophilia:

1.Oral Route (Tablets / Capsules)

Used mainly for long-term prevention of clot formation.

E.g : Apixaban

Rivaroxaban

2.Subcutaneous (SC) Route

Used for acute management, pregnancy, or when oral therapy is unsuitable.

E.g : Enoxaparin

Dalteparin

3. Intravenous (IV) Route

Used in hospital settings for severe or acute clotting events.

E.g : Streptokinase

Urokinase

Oral Delivery System:

The most popular, practical, and patient-friendly method of delivering medication is oral drug delivery. In order for medications to be absorbed in the gastrointestinal tract (GIT) and enter the systemic circulation, they must be administered orally. The capacity to create controlled- and sustained-release dose forms, convenience of administration, high patient compliance, and cost-effectiveness make oral delivery the favored method.

Advantages of Oral Delivery:

- High patient compliance
- Non-invasive and painless
- Safe and cost-effective
- Easy manufacturing and handling
- Suitable for controlled, sustained, or targeted release
- Large surface area in GIT for drug absorption

Limitations of Oral Delivery

- First-pass metabolism (liver) reduces drug bioavailability
- Degradation in stomach (acidic pH, enzymes)
- Variable absorption due to food, disease, GI motility
- Not suitable for large molecules like proteins/peptides
- Slow onset compared to IV

Factors Affecting Oral Drug Delivery

- Physicochemical properties (pKa, logP, solubility, stability)
- Physiological factors (gastric emptying, GI pH, enzymes)
- Food–drug interactions
- First-pass metabolism

Microsphere-BasedDrug DeliverySystems:

Microspheres are spherical particle carriers that are used to administer drugs in a targeted and regulated manner. Their diameter typically ranges from 1 to 1000 micrometres. For usage in pharmaceutical applications, drugs are contained in microspheres composed of biodegradable and biocompatible polymers.

Mechanism of Drug Entrapment in Microspheres

The polymer, preparation technique, and physicochemical characteristics of the medication all affect drug entrapment in microspheres. During the creation of microspheres, drug molecules are often integrated into or onto the polymer matrix through ionic, chemical, or physical interactions.

The major mechanisms are:

1.Polymer Matrix Formation (Polymer Solidification / Gelation)

When the polymer undergoes sol–gel transformation, crosslinking, or precipitation, the drug becomes trapped inside the polymer network.

2. Ionic Interactions (Electrostatic Binding)

Positively or negatively charged polymers interact with oppositely charged drug molecules.

Mechanism of Drug Release:

Drug release from microencapsulated products primarily occurs through diffusion, where the drug travels through pores or channels in the shell, but also via erosion (shell breakdown), swelling, osmosis, or chemical degradation of the polymer, often starting with a quick burst release from the surface followed by slower release as the matrix degrades or dissolves, all controlled by factors like polymer type, shell thickness, and environmental stimuli

(pH, enzymes).

FormulationTechniques:

Microspheres for oral antithrombotic drugare prepared using techniques that enable effective drug encapsulation, control of particle size, and the required release properties.Thekindofdrug,thepolymer,andtheintendeduseallinfluencethechoiceof formulation procedure. The methods most frequently used are as follows:

❖ **SolventEvaporation:**

Process:

A polymer and antifungal drug are dissolved in a volatile organic solvent to form the dispersed phase, which is then emulsified into an aqueous phase containing a stabilizer or surfactant. The solvent evaporates under stirring or reduced pressure, leading to polymer precipitation and formation of solid microspheres.

Advantages:

1. Suitableforhydrophobicdrugs.
2. Goodcontroloverparticlesize.
3. Relativelysimpleandscalable.

Limitations:

1. Useoforganicsolventsmayposetoxicityconcerns.

❖ **SprayDryingProcess:**

Asolutionorsuspensioncontainingthedrugandpolymerisatomizedintoahotair stream, rapidly drying droplets to form solid microspheres.

Advantages:

1. Suitableforheat-stabledrugs.
2. Producesuniformparticlesizedistribution.

Limitations:

1. Notsuitableforheat-sensitivedrugs.

❖ **Emulsificationandcross-Linkingprocess:**

Process

A polymer-drug solution is emulsified in an immiscible liquid, followed by cross- linking of the polymer to harden microspheres. Cross-linking agents (e.g., glutaraldehyde for chitosan or gelatin) are used to stabilize the microspheres.

Advantages:

1. Usefulfor naturalpolymers.
2. Allowscontroloversurfacepropertiesanddegradation.

Limitations:

Cross-linkingagentsmaycausetoxicity.

1. Requiresthoroughpurificationtoremoveresidualchemicals.
2.

❖ **CoacervationMethod:**

Process:

Polymeranddrugaredissolvedinasolvent;anon-solventortemperaturechange inducesphaseseparation,formingpolymer-richdropletsthatsolidifyintomicrospheres.

Advantages:

1. Canencapsulatebothhydrophilicandhydrophobicdrugs.
2. Producesuniformmicrospheres.

Limitations:

1. Processcomplexity.

EvaluationandCharacterizationofMicrosphere for Thrombophilia

Evaluation of microspheres is crucial to ensure safety, efficacy, and controlled drug release. The evaluation involves physicochemical, morphological, mechanical, and in vitro/in vivo tests.

1. **ParticleSizeandSizeDistribution**

Method:DynamicLightScattering(DLS),Laser

Diffraction,orOpticalMicroscopy

Importance:

Affects drug release rate, mucoadhesion, and absorption.

2. **SurfaceMorphology**

Method: Scanning Electron Microscopy (SEM) or Transmission Electron Microscopy (TEM)

Importance:

Spherical, smooth microspheres provide controlled release and better flow.

3. **EncapsulationEfficiency(EE%)andDrug Loading(DL%)**

Method:UV-Visible Spectrophotometryor HPLCafter microsphere dissolution.

EncapsulationEfficiency(EE%):

EE%Amountofdrugencapsulated/Totaldrug usedx100

DrugLoading(DL%):

DL%=Amountofdrugencapsulated/Totalwei ghtofmicrospherex100

Importance:

Determines how much drug is successfully incorporated into the microsphere.InVitroDrugReleaseStudies

Method: Dialysismembranediffusionmethod orFranzdiffusioncellusing phosphate buffer (simulated GI fluid)

Importance: Determines release kinetics and sustained-release behavior.

4. **Fourier-Transform Infrared Spectroscopy (FTIR)**

Purpose: Todetectpotentialinteractionsbet weendrugandpolymer.

Importance: Confirmsthechemicalintegrityo fthedrugafterencapsulation.

5. **DifferentialScanningCalorimetry(DSC) andX-RayDiffraction(XRD)**

DSC:Evaluatesthermalbehaviorandconfirm sthephysicalstate(crystallineor amorphous) of the drug in microspheres.

XRD:Identifieschangesindrugcrystallinity.

Importance:Helpsinpredictingthestabilityan ddissolutionbehaviorofthe formulation.

6. **Zeta Potential Measurement**

Method: Electrophoreticlightscattering

Importance:

Importance:

Determinesthesurfacechargeofmicrospher es.Ahigherabsolutezetapotential indicates better physical stability due to electrostatic repulsion.

7. **SwellingandErosionStudies(fornaturalp olymers)**

Purpose: Measures hydration capacity and degradation behavior of polymers in a moist environment (e.g. GI fluid).

Importance: Indicates water uptake and polymer behavior in GI fluids, affecting release.

8. **Flow Properties**

Importance: Affects uniformity in capsule/tablet filling and dosing.

- **Parameters:**

Bulk density, tapped density

Hausner ratio, Carr's index

Angle of repose

9. **Stability Studies**

Importance: Ensures shelf-life and drug integrity.

Conditions:

Room temperature, refrigerated, accelerated conditions (40°C ± 2°C / 75% RH)

- **Parameters Checked:**

Drug content

Physical appearance

Release profile

Conclusion:-

For the long-term treatment of thrombophilia, oral microsphere-based medication delivery devices present a viable and successful strategy. Microspheres help maintain steady therapeutic concentrations while reducing variations associated with traditional oral dose forms by delivering controlled, prolonged, and targeted release of anticoagulant medications. This lessens the risk of bleeding problems that are frequently associated with high peak plasma levels, increases patient compliance, and decreases the frequency of dose.

Polymers like chitosan, alginate, and HPMC improve mucoadhesion and intestinal absorption, increase drug stability, and shield the medication from deterioration in the gastrointestinal tract. Because of these characteristics, microspheres are especially useful for medications like contemporary anticoagulants that have low solubility, a short half-life, or restricted oral bioavailability.

All things considered, oral microspheres offer a sophisticated and user-friendly way to administer antithrombotic medications, and they have a great deal of promise to enhance thrombophilia treatment results. Their significance in anticoagulant therapy will be further strengthened by ongoing research on polymer optimisation, release kinetics, and in vivo performance.

References:

1. Dhadde GS, et al. A review on microspheres: Types, method of preparation, characterization and application, Asian Journal of Pharmacy and Technology; c2021. p.149-155. Available at: https://doi.org/10.52711/2231-57 13.2021.00025.
2. InternationalJournalofRecentScientificResearch"(nodate).Availableat:https://doi.org/10.24327/ijrsr.
3. KH R. Microspheres: As Carrieres used for Novel Drug Delivery System, IOSR Journal of Pharmacy (IOSRPHR).2012;2(4):44-48. Available at: https://doi.org/10.9790/3013-24204448.
4. Nirav R patel, Dhagash A patel, Praful D Bharadia, Vikram pandya, Darshan modi. Microsphere as a novel drug delivery; c2011. p. 992-997.
5. Rosendaal FR. Causes of venous thrombosis. Thromb J. 2016;14(Suppl 1):24.
6. Lijfering WM, Rosendaal FR, Cannegieter SC. Risk factors for venous thrombosis. Curr OpinHematol. 2015;22(5):436–43.
7. Aulton ME, Taylor KM. Aulton's Pharmaceutics: The Design and Manufacture of Medicines. 5th ed. London: Elsevier; 2018.
8. Dixit N, Maurya SD, Bhargava A. Oral sustained release drug delivery systems. Int J Curr Pharm Res. 2011;3(1):12–8.

9. Tripathi KD. 2008. Essentials of Medical Pharmacology, 6th Edition. Jaypee Brothers Medical Publishers (P) Ltd.
10. Forbes NS, Peppas NA. Oral delivery of pharmaceuticals: challenges and opportunities. Drugs Pharm Sci. 2005;148:1–19.
11. Rao MRP, Reddy VB, Sravani B. Overview on microspheres: formulation and evaluation. J Glob Trends Pharm Sci. 2013;4(3):1248–58.
12. Gómez-Outes A, Suárez-Gea ML, Lecumberri R, Terleira-Fernández AI, Vargas-Castrillón E. Direct oral anticoagulants in the treatment of venous thromboembolism: A systematic review. Thromb Res. 2014;134(4):774–82.
13. Tadic L, Müller RH. Pharmaceutical microspheres: Production, processing, and characterization. Drug Dev Ind Pharm. 1998;24(12):1133–44.
14. Chaturvedi M, Kumar M, Pathak K. A review on mucoadhesive microspheres as an innovative drug delivery system. Int J Pharm Sci Res. 2011;2(9):2242–55.
15. Pandey S, Gopal M, Rai AK. A review on microsphere for novel drug delivery system. Int J Pharm Res Biosci. 2013;2(2):204–17.
16. Kumar R, Prasad SB, Patra S. Formulation and evaluation of chitosan microspheres for controlled delivery of drug. Asian J Pharm Clin Res. 2012;5(3):66–8.
17. Dai B, Li L, Zhang Y, Liu J, Zhong L, Zhao H. Novel microspheres reduce the formation of deep venous thrombosis and repair the vascular wall in a rat model. Blood Coagul Fibrinolysis. 2017;28(5):398-406.
18. Xiao S, Sun X, Wang C, Wu J, Zhang K, Guo M, et al. Nanomicrosphere sustained-release urokinase systems with antioxidant properties for deep vein thrombosis therapy. RSC Adv. 2024;14:7195-7205.
19. Ye W, Wang N, Zhang Y, Chen J, Wu H. Bio-inspired microcapsule for targeted antithrombotic drug delivery. RSC Adv. 2018;8:27253-27259.
20. Furie B, Furie BC. Mechanisms of thrombus formation. N Engl J Med. 2008;359(9):938-949.
21. Torchilin VP. Multifunctional and stimuli-sensitive pharmaceutical nanocarriers. Eur J Pharm Biopharm. 2009;71(3):431-444.