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MICROENCAPSULATION: A REVIEW ON POLYMERS AND CORRELATION WITH BCS CLASSIFICATION OF DRUGS

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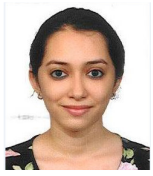
ABSTRACT

Microencapsulation has evolved in the last decade to become a frontrunner in the delivery of drugs. With the ever increasing drugs being synthesized, the number of polymers to coat it and help with their stability has also increased. This review describes the need for this process and the different aspects of the process of Microencapsulation and provides a glimpse into the various techniques of this process and the variety of polymers in use. This review comprises of a tabulation of a literary survey of the researches on microencapsulation of the various drugs, their BCS classification and the polymers used to encapsulate the drugs.This tabulation aids in establishing a correlation between the BCS classification of the drug and the polymer used to serve the purpose of microencapsulation.

KEYWORDS: Microencapsulation, Techniques, BCS classification, Ethyl Cellulose, Eudragit®



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INTRODUCTION

Microencapsulation is the process by which tiny particles or droplets or gaseous molecules of active ingredients are coated or surrounded by a continuous film of a second material to produce a formulation having modified or enhanced pharmacokinetic properties. The material to be coated or the active ingredient is called the core or fill or internal phase. The second material used to surround the core material is often called the shell or coating material or membrane. It is generally accepted that microencapsulation products (microparticles) are more than 1 micrometer in diameter and can be up to 1000 micrometer as well. Commercially, Microparticles diameter ranges from 3 to 800 micrometer and can contain 10% to 90% w/w core material.

NEED

Microencapsulation has shown to achieve useful properties for the core material/ active ingredient that have helped with the drug's stability, therapy or compliance.
Some of the reasons for employing microencapsulation of a drug are:

- To mask organoleptic properties of the drug, such as, taste and odor, to help improve patience compliance of the drug. Eg. Paracetamol, Nitrofurantoin- masking their bitter taste.
- To convert liquid drugs into free flowing powder to help improve the drug's stability and increase ease of processing. Eg. Eprazinone.
- To protect sensitive drugs from moisture, light and air(oxygen) and increase their stability. Eg. Nifedipine-protected from photo instability.
- To separate incompatible moieties/drugs from each other.
- To prevent vaporization of volatile drugs at room temperature. Eg. Aspirin, Peppermint oil- are volatile at room temperature.
- To reduce toxicity or other reactions, such as, GI irritation. Eg.-KCl, Ferrous sulphate, Aspirin(GI irritation).
- To change site of absorption in case of drugs that may be toxic or unstable at a certain pH but less toxic and stable at a different pH.
- To control the release of active ingredient, by either Sustained or Delayed release, to help increase the duration of therapy of the drug.
- To perform targeted release of drug.

DISADVANTAGE

- It is a complex procedure.
- A lot of study and research needs to be carried to select the right coating material and the appropriate technique of manufacture so that microparticles of appropriate properties and dimensions can be achieved.
- It is a costly process- not economical
- It involves a lot of skill. Thus, involvement of only skilled workers.
- It is difficult to get continuous and uniform film on each and every particle or droplet.

MICROENCAPSULATION FORMULATIONS

The Microencapsulated drug or ingredient can be used to form different types of formulation.
Here are some formulations:

- Tablets
- Capsules
- Lotion
- Dry Powder

- Parenteral
- Suspensions
- Emulsions

BIOPHARMACEUTICS CLASSIFICATION SYSTEM

Microencapsulation is a method of delivering drugs with modified properties to achieve the required pharmacokinetics. Some of the applications of microencapsulation include Control release of drug, Delayed release of drug, Targeted release of drug, Reduce Gastric Irritation, Increase stability of drug.To modify the drug to achieve any of the above properties, it is necessary to know the drug's class under the Biopharmaceutics Classification System. Biopharmaceutics Classification System (BCS) has provided a systematic approach to understanding the concept of drug absorption in terms of permeability and solubility. It is a system of classification that sets out to differentiate the drugs on the basis of parameters like, their solubility and permeability. According to the Biopharmaceutics Classification System, drug substances are classified in the following manner:

- Class I - high permeability, high solubility
- Example: Metoprolol
- These compounds are well-absorbed and their absorption rate is usually higher than excretion.
- Class II - high permeability, low solubility
- Example: Glibenclamide, Bicalutamide, Ezetimibe
- The bioavailability of these products is limited by their solvation rate. A correlation between the in-vivo bioavailability and the in-vitro solvation can be found.
- Class III - low permeability, high solubility
- Example: Cimetidine
- The absorption is limited by the permeation rate, but the drug is solvated very fast. If the formulation does not change the permeability or gastro-intestinal duration time, then class I criteria can be applied.
- Class IV - low permeability, low solubility
- Example: Hydrochlorothiazide
- These compounds have a poor bioavailability. Generally, they are not well absorbed over the intestinal mucosa and a high variability is to be expected.

The drugs are classified in BCS on the basis of the following three parameters:

1. Solubility
2. Permeability
3. Dissolution

Of the 130 orally available medicines on the WHO's EML (Essential Medicines List-April, 2002):-

- 64 were classified reliably by the FDA
- 25 were classified provisionally by the FDA
- 41 could not be classified unambiguously, but could be narrowed down on two classes, by the FDA

TECHNIQUES OF MICROENCAPSULATION

Preparation of micro-particles should satisfy certain criteria:

- The ability to incorporate reasonably high concentrations of the drug.
- Stability of the preparation after synthesis with a clinically acceptable shelf life.
- Controlled particle size and dispersability in aqueous vehicles for injection.
- Release of active reagent with a good control over a wide time scale.

- Biocompatibility with a controllable biodegradability and Susceptibility to chemical modification.

The method of preparation and the techniques employed for microencapsulation overlap considerably.The choice of polymer plays an important role in selecting the technique of microencapsulation Thus, appropriate combination of starting materials and synthesis methods can be chosen to produce microencapsulated products with a wide variety of compositions and morphological characteristics.

Some of these microencapsulation techniques are enlisted below**:**

- Air-suspension coating
- Coacervation and phase separation
- Polymer encapsulation by rapid expansion of supercritical fluids **:**
  - Rapid expansion of supercritical solution
  - Gas anti-solvent (GAS) process
  - Particles from a gas-saturated solution (PGSS)
- Centrifugal extrusion
- Multiorifice Centrifugal process
- Pan coating
- Spray–drying and Spray-congealing
- Fluidized-bed technology
- Solvent evaporation**:**
  - Single Emulsion Method
  - Double Emulsion method
  - Polymerization
  - Interfacial polymer

POLYMERS USED IN MICROENCAPSLATION

Poly(meth)acrylates – Eudragit®.

Whether one needs their drug to be released over a specific period of time, or would like it to benefit from the advantages of multi-particulate or matrix formulations, Eudragit® polymers can help one achieve their desired drug release profile. Drug delivery can be controlled throughout the entire gastrointestinal tract to increase therapeutic effect and patient compliance. Different polymer combinations of Eudragit® RL and RS grades allow custom-tailored release profiles to achieve the desired drug delivery performance. Eudragit® NE and NM grades are neutral ester dispersions which do not require additional plasticizers.

Benefits from Eudragit® coatings include**:**

-Time-controlled release of active ingredients

-Therapeutically customized release profiles

-Higher patient compliance due to reduced number of doses to be taken

-Cost-effective processing

TABLE 1
Eudragit® Products

Polymer	Availability	Dissolution Properties
EUDRAGIT® RL 100	Granules	Insoluble **High permeability** pH-independent swelling
EUDRAGIT® RL PO	Powder	
EUDRAGIT® RL 30 D	30% Aqueous Dispersion	
EUDRAGIT® RL 12,5	12,5% Organic Solution	
EUDRAGIT® RS 100	Granules	Insoluble **Low permeability** pH-independent swelling
EUDRAGIT® RS PO	Powder	
EUDRAGIT® RS 30 D	30% Aqueous Dispersion	
EUDRAGIT® RS 12,5	12,5% Organic Solution	
EUDRAGIT® NE 30 D	30% Aqueous Dispersion	Insoluble, low permeability, pH-independent swelling **No plasticizer required** Highly flexible
EUDRAGIT® NE 40 D	40% Aqueous Dispersion	
EUDRAGIT® NM 30 D	30% Aqueous dispersion	

Ethyl Cellulose

Ethyl cellulose is a derivative of cellulose in which a defined percentage of the hydroxyl groups of the repeating glucose units are substituted with ethyl ether groups. Ethyl cellulose is an inert, hydrophobic polymer, and is tasteless, odorless, colorless, non-caloric, and physiologically inert. It has long been used as a solvent-based tablet and pellet coating, as a tablet binder, to prepare microcapsules and microspheres, and both as film- and matrix-forming material for sustained-release dosage forms. Ethyl cellulose organic solutions are often used for both hydrophobic film coating and controlled release coating of solid dosage forms. Ethyl cellulose is used to mask an unpleasant taste or to improve the stability of a formulation. Films are dense and suitable for humidity protection and provide very long-lasting release kinetics. Ethyl cellulose is widely used in pharmaceutical film coating because it forms strong films with good adhesion.

Table 2
Ethyl Cellulose Products

Ethyl Cellulose: Products			
Description	**Grade**	**Solution Viscosity Range (mOas)**	**EthoxylContent (%)**
Ethyl Cellulose	10	08-12	47.5-49.5
	20	18-22	
	50	40-60	
	70	56-84	
	100	80-120	

Hydroxy Propyl Methyl Cellulose

Hydroxy propyl methylcellulose (HPMC) is a semisynthetic, inert, viscoelastic polymer. Hydrophilic matrices containing hydroxyl propyl methylcellulose (HPMC) are a principal technology used for extended release (ER) oral dosage forms. It is very suitable to be used as a retardant material in CR matrix dosage forms, as it is nontoxic and easy to handle. HPMC confers ER properties by rapidly forming a viscous layer (commonly termed the 'gel layer') of hydrated polymer on the matrix surface on contact with aqueous liquids. This acts as a physical and diffusion barrier to the rate of water ingress and the diffusional/erosional release of drug. Different drugs show different release profile with different grades but most often show an increase in release with decreasing viscosity.

Kollidon

Kollidon SR is a blend of polyvinyl acetate and povidone (K 30) in the ratio of 8:2, used in the pharmaceutical industry as a matrix-forming agent. It is particularly suitable for the manufacture of pH-independent sustained-release matrix dosage forms. Polyvinyl Acetate is a very plastic material that produces a coherent matrix. When these tablets are introduced into gastric or intestinal fluid, the water soluble povidone is leached out to form pores through which the active ingredient slowly diffuses outwards. It contains no ionic groups, hence, is inert to drug substance. The sustained release properties are unaffected by ions or salts.

Cyclodextrin

One of the important characteristics of Cyclodextrin is that they form inclusion complexes both in solution and in the solid state, in which each guest molecule is surrounded by the hydrophobic environment of the CD cavity. This can lead to alteration of physical, chemical and biological properties of guest molecules, and can eventually have considerable pharmaceutical potential.

Other Polymers used in Microencapsulation

Cellulose Acetate Phthalate

Cellulose acetate phthalate (CAP), also known as cellacefate or cellulosiacetasphthalas, is a commonly used polymer phthalate. It is a hygroscopic, white to off-white free-flowing powder, granules, or flakes. CAP has a special ability to withstand acidic pH in stomach, but it readily dissolves in slight alkaline medium of small intestine.

Advantages of CAP film coating include:

-Enhanced palatability by masking unpleasant tastes or objectionable odors
-Ease ingestion/swallowing
-Improve product appearance
-Protect tablets from light, oxidation & moisture
-Advance the perception of superior product efficacy

Cellulose Acetate Butyrate

When cellulose is esterified with both acetyl and butyryl radicals to form the mixed ester, cellulose acetate butyrate, many of the desirable properties of both esters are obtained.

Hydroxy Propyl Methyl Cellulose Phthalate (HPMCP)

HPMCP is an enteric coating agent, i.e., it is used to protect drugs from degradation by gastric acid or to prevent them from causing side effects in the stomach. HPMCP was originally developed and used as an enteric coating agent. Now, its favorable properties have led to its use for a range of applications in other fields, including sustained release preparations, binders and microcapsule bases. HPMCP is usually used alone, but can be used in combination with other polymers, as in the case of the sustained release preparations.

TABULATION OF LITERARY SURVEY: Correlation of BCS Classification of Drug and Coating Polymer used in the drug's Microencapsulation

Keeping in mind all the techniques and polymers mentioned before, here is a compilation of drugs that have been microencapsulated due to one or more than one reason using the above mentioned methods and polymers. These microcapsules or microspheres are either already in market or still under research, but their microencapsulated formulation has been developed to enhance or modify the drug's

pharmacokinetic properties. In the following compilation the drug and the different techniques used to microencapsulate the drug along with the coating polymer have been listed.

TABLE 3
LITERARY SURVEY

DRUG	BCS CLASS OF DRUG	COATING POLYMER	TECHNIQUE OF MICROENCAPSULATION
ASPIRIN [2,3]	III	ETHYL CELLULOSE	(O/W) SOLVENT EVAPORATION
FOLIC ACID[3]	II/IV	ETHYL CELLULOSE	(O/O) SOLVENT EVAPORATION
AMOXICILLIN[3]	III	ETHYL CELLULOSE	SOLVENT EVAPORATION
DICLOFENAC SODIUM[3,4]	II	ETHYL CELLULOSE	SOLVENT EVAPORATION
DICLOFENAC SODIUM[3,5]	II	ETHYL CELLULOSE	COACERVATION
ZIDOVUDINE[3,5]	I	ETHYL CELLULOSE	SOLVENT EVAPORATION
FLUCONAZOLE[3,5]	I	ETHYL CELLULOSE	SOLVENT EXTRACTION
SALBUTAMOL SULPHATE[5]	I	ETHYL CELLULOSE	COACERVATION
NIMESULIDE[5]	II	ETHYL CELLULOSE	MODIFIED SOLVENT EVAPORATION
INDOMETHACIN[5]	II	ETHYL CELLULOSE	SOLVENT EVAPORATION
LAMIVUDINE[5]	III	ETHYL CELLULOSE	SOLVENT EXTRACTION
METRONIDAZOLE[5]	I	ETHYL CELLULOSE	COACERVATION
ONDANSTERON[5]	I	ETHYL CELLULOSE	SOLVENT EXTRACTION
CEFADROXIL[5]	III	ETHYL CELLULOSE	SOLVENT EXTRACTION
CEPHRADINE[5]	III	ETHYL CELLULOSE	SOLVENT EXTRACTION
ACECLOFENAC[5]	II	ETHYL CELLULOSE	SOLVENT EXTRACTION
SALBUTAMOL SULPHATE[6]	I	ETHYL CELLULOSE	EMULSION SOLVENT EVAPORATION
CAPTOPRIL[3,7]	III	ETHYL CELLULOSE	TEMPERATURE INDUCED COACERVATION
HYDROXYZINE HCl[8]	I	ETHYL CELLULOSE	TEMPERATURE INDUCED COACERVATION
TRAMADOL HCl[9]	I	ETHYL CELLULOSE	SPRAY DRYING
ZIDOVUDINE[3,5,10]	I	ETHYL CELLULOSE	DOUBLE EMULSION SOLVENT DIFFUSION
ACYCLOVIR[11]	III	ETHYL CELLULOSE	SOLVENT EVAPORATION
METFORMIN HCl[12]	III	ETHYL CELLULOSE	NON SOLVENT ADDITION COACERVATION
PSEUDOEPHEDRINE[13]	III	ETHYL CELLULOSE	O/W OR W/O SOLVENT EVAPORATION
RANITIDINE HCl[5,14]	III	ETHYL CELLULOSE	SOLVENT EXTRACTION
INDOMETHACIN[15]	II	ETHYL CELLULOSE	COACERVATION
BACAMPICILLIN [16]	II/IV	ETHYL CELLULOSE	TEMPERATURE INDUCED COACERVATION
METFORMIN HCl[16]	III	ETHYL CELLULOSE	DOUBLE EMULSION SOLVENT DIFFUSION
ALLOPURINOL[17]	I	ETHYL CELLULOSE	SOLVENT EVAPORATION
ADRIAMYCIN HCl[18]	III	ETHYL CELLULOSE	COACERVATION

CISPLATIN[19]	IV	ETHYL CELLULOSE	COACERVATION
DILTIAZEM HCl[20]	I	ETHYL CELLULOSE	W/O EMULSION SOLVENT EVAPORATION
ISOSORBIDE DINITRATE[21]	I/III	ETHYL CELLULOSE	SOLVENT EVAPORATION
NAPROXEN[22]	II	ETHYL CELLULOSE	COACERVATION
TERBUTALINE SULPHATE[23]	II	ETHYL CELLULOSE	COACERVATION
STAVUDINE[24]	I	ETHYL CELLULOSE	W/O/O DOUBLE EMULSION SOLVENT DIFFUSION
STAVUDINE[24]	I	ETHYL CELLULOSE + POLYVINYL PYRROLIDONE	W/O/O DOUBLE EMULSION SOLVENT DIFFUSION
IBUPROFEN[25]	II	ETHYL CELLULOSE +POLYSTYRENE	SOLVENT EVAPORATION
PROPANOLOL HCl[26]	I	ETHYL CELLULOSE + CELLULOSE ACETATE PHTHALATE	COACERVATION
PROPANOLOL HCl[26]	I	CELLULOSE ACETATE PHTHALATE	COACERVATION
DICLOFENAC SODIUM[27]	II	Eudragit® RS 30 D +ETHYL CELLULOSE (SURERELEASE)	SPRAY DRYING
PREDNISOLONE[28]	I	Eudragit® E + ETHYL CELLULOSE	SOLVENT EVAPORATION
CHLOROQUINE DIPHOSPHATE [29]	I	Eudragit® RS100	NON-SOLVENT ADDITION COACERVATION
IBUPROFEN[30]	II	Eudragit® RS100	EMULSION SOLVENT DIFFUSION
IBUPROFEN[31]	II	Eudragit® L-100-55	COACERVATION
ACECLOFENAC[32]	II	Eudragit® S100	O/W EMULSION SOLVENT EVAPORATION
ACECLOFENAC[32]	II	Eudragit® RL100	O/W EMULSION SOLVENT EVAPORATION
ACECLOFENAC[32]	II	Eudragit® RS100	O/W EMULSION SOLVENT EVAPORATION
DILTIAZEM HCl[33]	I	Eudragit® RL100	SPRAY DRYING
DILTIAZEM HCl[33]	I	Eudragit® RS100	SPRAY DRYING
PIROXICAM[34]	II	Eudragit® S100	EMULSION SOLVENT EVAPORATION
THEOPHYLLINE[34]	I	Eudragit® S100	EMULSION SOLVENT EVAPORATION
CEFUROXIME AXETIL[35]	II	Eudragit® L-55	SOLVENT EVAPORATION
CEFUROXIME AXETIL[35]	II	Eudragit® RL100	SOLVENT EVAPORATION
CEFUROXIME AXETIL[35]	II	Eudragit® E	SOLVENT EVAPORATION
STAVUDINE[36]	I	Eudragit® RS100	SOLVENT EVAPORATION
STAVUDINE[37]	I	Eudragit® RL100	SOLVENT EVAPORATION
KETOROLAC	I	Eudragit® S100	NON SOLVENT ADDITION INDUCED

TROMETHAMINE[38]			COACERVATION
5-AMINOSALICYCLIC ACID[39]	IV	Eudragit® RS	SOLVENT EVAPORATION
BACAMPICILLIN [40]	II/IV	Eudragit® E	SOLVENT EVAPORATION
NITRENDIPINE[41]	II	Eudragit® RL100	EMULSION SOLVENT EVAPORATION
CHLORPHENIRAMINE MALEATE[42]	I	Eudragit®S100	DOUBLE EMULSION SOLVENT DIFFUSION
CHLORPHENIRAMINE MALEATE[42]	I	Eudragit®L100	DOUBLE EMULSION SOLVENT DIFFUSION
CHLORPHENIRAMINE MALEATE[42]	I	Eudragit®L100-55	DOUBLE EMULSION SOLVENT DIFFUSION
SODIUM PANTOPRAZOLE[43]	III	Eudragit® S100	SOLVENT EVAPORATION
SODIUM PANTOPRAZOLE[43]	III	Eudragit® S100	SPRAY DRYING
GLIPIZIDE[44]	II	Eudragit® RS100	EMULSION SOLVENT EVAPORATION
DIFLUNISAL[45]	II	Eudragit® RS100	SOLVENT EVAPORATION
DIFLUNISAL[45]	II	Eudragit® RL100	SOLVENT EVAPORATION
VERAPAMIL HCl[46]	I	Eudragit® RS100	COACERVATION
VERAPAMIL HCl[46]	I	Eudragit® RL100	COACERVATION
ALBENDAZOLE SULFOXIDE[47]	II	Eudragit® RS PO	SOLVENT EVAPORATION
KETOPROFEN[48]	II	Eudragit® RL 30D	SPRAY DRYING
SODIUM NAPROXEN[49]	II	Eudragit® RS	COACERVATION
ACYCLOVIR[50]	III	Eudragit® S100	EMULSION SOLVENT EVAPORATION
RITONAVIR[51]	II	Eudragit® S100	SOLVENT EVAPORATION
TINIDAZOLE[52]	II	Eudragit® RS PO	EMULSION NON SOLVENT ADDITION COACERVATION
PIOGLITAZONE[53]	II	Eudragit® E100	COACERVATION
METOPROLOL TARTARATE[54]	I	Eudragit® RS100	SOLVENT EVAPORATION
GLIBENCLAMIDE[55]	II	Eudragit® RL PO	EMULSION- SOLVENT EVAPORATION
SALBUTAMOL SULPHATE[56]	I	Eudragit® RS100 + Eudragit® RL100	SOLVENT EVAPORATION
NIFEDIPINE[57]	II	Eudragit®	SOLVENT EVAPORATION
NITROFURANTOIN[58]	II	CARBOXYMETHYL CELLULOSE +GELATIN	COMPLEX COACERVATION
AMOXICILLIN TRIHYDRATE[58]	III	CARBOXYMETHYL CELLULOSE +GELATIN	COMPLEX COACERVATION

CONCLUSION

From the above mentioned literature survey, we can conclude that Ethyl Cellulose is the preferred choice of polymer for microencapsulation. Ethyl cellulose has been studied for all the types of drugs as per their BCS classification. The next most widely studied polymer is Eudragit® RS100 but its use has been explored mostly for drugs of Class I

and class II as per BCS classification. The potential of Eudragit® S100 has been explored bya few scientists and has been used for preparation of microcapsules for Class I, Class II and Class III but its potential of use for Class IV has remainmostly unexplored. From above literature survey, we can fairly conclude that Ethylcellulose is the indispensable choice for microencapsulation, followed by Eudragit RS100, S100 and RL100. Another observation is that,till date, the drugs chosen for Microencapsulation are mostly belonging to BCS Class I and BCS Class II. [59]Since class I comprises of drugs that have high solubility and high permeability, the purpose of choosing the Ethyl cellulose and Eudragit can be reasoned to be to retard the release of the drug, in order to minimize the dosing frequency. [60]Class II comprises of drugs that have low solubility and high permeability. These drugs get easily eliminated from the site of absorption as the dissolution rate is slow. This may result in its reduced bioavailability. Thus, to enhance the bioavailability of these drugs, they can be microencapsulated with release retarding polymers. Class III comprises of drugs that have high solubility and low permeability and these drugs are absorbed and released via active transport permeation. Thus, they can be microencapsulated by retarding polymers to enhance their absorption.

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