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A Concise Understanding of Pharmaceutical Excipients

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ABSTRACT

Excipient are indispensable component of medicinal dosage forms and in most of the formulations they are present in greater proportion in comparison to the active pharmaceutical ingredient, as it forms the bulk of the formulation it is necessary to choose an excipient which satisfies the ideal properties for a particular excipient. Various excipient compatibility tests are performed that gives the manufacturer an idea of the proper choice of the excipients to avoid any interaction or unwanted happenings. The proper choice of excipients are dependent upon various factors like the physical and chemical properties and various other factors associated with the drug including the route of drug delivery. Excipients are classified based upon the function they perform, however several excipients behave differently at different concentrations also one excipient can be used for multiple purposes depending upon the need of the dosage form, e.g.: When 5% starch is used in formulation it acts as a binder for tablet formulations whereas when it is used in dry form it can perform the function of a disintegrant. The key to a successful pharmaceutical formulation is to have knowledge of API, excipients, their interaction and process parameters.

INTRODUCTION

The prime objective of a pharmaceutical dosage form is to deliver drug to the patient in the needed amount, at the required rate, consistently within a batch, from batch to batch, and over the product's shelf life. To produce a drug substance in a final dosage form requires pharmaceutical ingredients [1]. While choosing the required excipients the formulator must be aware of the existing standards which are available to ensure the proper quality and consistency of the excipients from lot to lot. Various non-active agents that are added into the pharmaceutical entity during the development of the dosage forms like tablets, capsules, suppositories and injections, don't have any therapeutic value but are needed to affect the functioning of the active pharmaceutical agent and the dosage form at large. Inactive ingredients may also be considered as inert ingredients or excipients, generally having no pharmacological effect [2]. However, not all non-active ingredients are always inactive. Alcohol is one example of an ingredient that may be active or inactive based on the specific formulation of the medication. Medicines contain ingredients other than the active drug that are essential for their manufacturing, stability and function [3]. These compounds (excipients) are generally added along with the active pharmaceutical ingredients for:

- Protection, support or stability of the formulation.
- Bulking up the formulation in case of potent drug for assisting in formulation of an accurate dosage form.
- Improve patient acceptance.
- Help in improving bioavailability of active drug.
- Enhancing overall safety and effectiveness of the formulation during its storage and use.

PURPOSE

The following study describes the utility of excipients, classification and factors for the choice of the most suitable excipient also the dose response relationship of various excipient is looked into proper justification.

BACKGROUND

Excipients form the major part of a drug formulation. These adjuvants are most commonly used in various drug preparations where physical attributes of the pharmaceutical entity including particle size is of great importance. The formulator is mainly responsible to identify the desired physical characteristics that must be inflicted into the preparation via use of appropriate excipients, it becomes the sole responsibility of the excipient manufacturer to develop the excipients in precise environmental conditions and adequate manufacturing parameters so that the yield is uniform in consistency and posses the exact qualities [4]. usually excipients form a major bulk of the medicinal product and in many preparations they exceed the percentage to twice or three folds when compared to that of the Active Pharmaceutical Agent (API), hence care must be taken in proper selection of the excipients both qualitatively and quantitatively as selection of non-compatible excipient or selection of a precise excipient in wrong quantity both may lead to the failure of the resultant dosage form so excipients must be selected based on the properties it offers and only those are chosen which posses the required ideal properties and hold good for the formulation [5]. It is for this reason excipient compatibility tests are carried out; these tests give the idea to the formulator about any possible excipient interaction, any such issues if found out, can be dealt by the formulator and required modifications/alterations are made. The choice of proper excipients other than route of drug delivery, depends upon various characteristics of them including functionality, regulatory acceptance, consistency of the material, sources, cost and availability physicochemical properties, stability and compatibility issues, pharmacokinetic parameters, permeation characteristics, segmental absorption behavior, drug delivery platform, intellectual property issues etc., these characteristics are of greater importance in designing of the most suitable delivery platform. The concept of quality by design (QbD) helps in understanding excipients normal variability and its potential impact on the processes of formulation development can be achieved [6].

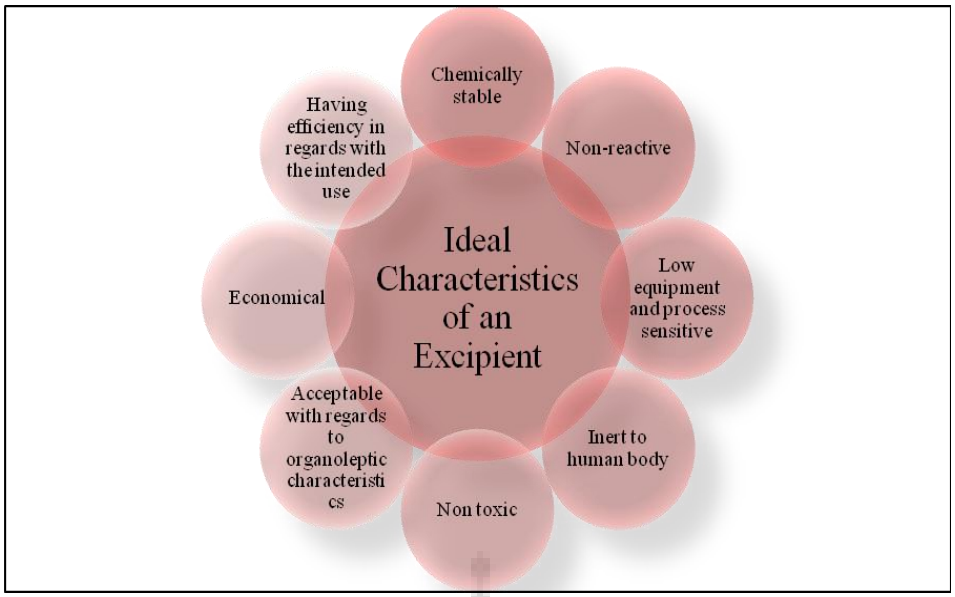

Figure 1: Characteristics of an ideal Excipient

SELECTION CRITERIA FOR SUITABLE EXCIPIENTS

Excipients used in the pharmaceutical dosage forms may have a variety of function to perform. They may be added to maintain the integrity of the dosage form, make up the volume of the dosage form, aid in the release characteristics of the dosage form, provide taste, or to aid in the formulation pattern of the dosage form. Depending on the role and compatibility the most suitable excipient is chosen, however care must be taken in the selection criteria of the excipient as only those excipients needs to be chosen which holds good for the final dosage form that is to be made, be it of any kind, otherwise at some point or the other either during the formation of the dosage form some untoward happening like improper hardness, friability issues, non-uniform weight etc. is sure to happen or, excipients at times, are used to affect the release of the API, any mistake in the selection process of the excipient may lead to an earlier release of the API in the assimilation process leading to tissue damage and gastric discomfort[7].

Pharmaceutical Excipient Factors Affecting Tablet Formulation

Excipient Functionality –Can only be properly assessed in the context of a particular formulation and manufacturing process. Functionality is linked inextricably to the formulation and process and all formulations are different.

Excipient Grades –Several major pharmaceutical excipients are available in different grades. These grades are a representation of their physical and chemical characteristics. Similar excipient of different grades shows variability in performance.

Impurity Profile –Basically excipients may contain a concomitant entity along with the main excipient this concomitant entity plays a major role in the functioning of the excipient it may not have any chemical effect but these excipients may be necessary in ensuring the proper behavior of the excipient, any other foreign substance present in the excipient may be termed as an impurity. The presence of impurities may at times hinder the proper behavior of the excipient. These impurities may be organic, inorganic and/or residual solvents [8].

Formulation Design –The formulation must be designed so as to obtain the required result however using lesser number of excipients has its' own benefits as:

- A completely inert excipient is impossible. Various studies and investigations have revealed that even some of the most widely used excipients which are considered pharmaceutically inactive or non-toxic may lead to adverse reactions.
- Lesser constituents may lead to lesser influence upon the product consistency and involved manufacturing process.
- Less capital investments.
- Lesser number of excipient would gradually decrease the chances of any kind of interaction between the API and the excipient or among excipient itself.

Drug-Excipient and Excipient-Excipient Interaction –Several processes namely adsorption, complexation, changes in pH, formation of eutectic mixture and/or various chemical interaction results in alteration of the dosage form, these may yield in either unstable dosage formation or may produce potentially harmful entities rendering the entire pharmaceutical dosage form unsafe/useless, as in case of several acidic and basic drugs where, according to Henderson – Hasselbalch Equation, the microenvironment pH gets influenced upon the interaction of Acidifiers (Citric Acid, Tartaric Acid, Malic Acid, Fumaric Acid, etc.) and Alkalinizing agents (Sodium Bicarbonate, Sodium Carbonate, Magnesium Oxide, etc.) however at times it is this excipient-excipient interaction which is utilized as a formulation strategy to obtain products of suitable attributes (E.g. Viscosity of Xanthan gum is increased in the presence of Ceratonia) [9].

Other factors –To ensure the desired yield, while designing a formula, the formulator is also expected to keep in mind various other factors like physiochemical properties, stability and compatibility issues, pharmacokinetic attributes, permeation characteristics, segmented absorption behavior, drug delivery platforms, intellectual property issues and marketing drive [10].

Excipient Selection and Criteria for Injectable Dosage Forms

Development of injectables require a thorough understanding of the type and quality of excipient to be used as any such formulation would come into direct contact with the vital organs of the body the choice of excipient for injectables also depends upon the routes of drug delivery [11].

Excipients used to prepare injectables have to hold good with various stringent requirements. It is required that the formulator or the manufacturer must not only ensure the purity and authenticity of the excipients (via various analytical techniques like infrared spectrophotometry and chromatography) but also identify the limits for impurity. It is to be confirmed that these limits must be based on the appropriate toxicological data or the limits mentioned in national compendia requirements. Care must also be maintained while the manufacturing processes of injectables to avoid any accidental contamination. If the injectables are derived from natural source the level of endotoxins needs to be checked and further testing for Bovine Spongiform Encephalopathy (BSE) needs to be carried out [12].

CLASSIFICATION OF MAJOR EXCIPIENTS BASED ON THEIR FUNCTIONS [10-13]

Excipients are classified according to their functions [13] as:

- Binders- Which are used to maintain the integrity of the dosage form.
- Disintegrants- Used to facilitate the disintegration or the breaking up of the dosage form.
- Fillers (diluents)- Used to adjust the volume of the dosage form.
- Lubricants- Aid in the manufacturing process so that the load moves through the machines.
- Glidants- Avoids sticking of the load to punches and facilitates movement.

- Compression aids- Assist in compression.
- Colors- To add coloration.
- Sweeteners- To add taste or enhance mouth feel.
- Preservatives- To enhance shelf life of the dose.
- Flavors- Taste
- Film formers/coatings- Used in several dosage forms to affect the release profile of the dose.
- Suspending/dispersing agents/surfactants- To affect the inter particle surface tension.

Since excipients are versatile in nature and their behavior, at times, may depend upon their concentration.

Excipient behavior at different concentration:

Table 1: Excipient and its function at different concentration

Sr. No	Excipient	Concentration (%)	Behavior	Other Uses	Reported Incompatibility with
1	Acacia [14], [15], [16]	10–20	Emulsifying agent	viscosity-increasing agent	amidopyrine, apomorphine, cresol, Ethanol (95%), ferric salts, morphine, phenol, physostigmine, tannins, thymol, and vanillin.
		10–30	Pastille base		
		5–10	Suspending agent		
		1–5	Tablet binder		
2	Bentonite [17]	1.0–2.0	Adsorbent (clarifying agent)	viscosity-increasing agent	strong electrolytes, acriflavine hydrochloride
		1.0	Emulsion stabilizer		
		0.5–5.0	Suspending agent		
3	Benzoic Acid [18]	0.17	IM and IV injections	Antimicrobial preservative; therapeutic agent.	Alkalis or Heavy metals. Preservative activity may be reduced by interaction
		0.01–0.1	Oral solutions		
		0.1	Oral suspensions		

		0.15	Oral syrups		with kaolin.
		0.1–0.2	Topical preparations		
		0.1–0.2	Vaginal preparations		
4	Butylparaben	0.006–0.05	Oral suspensions	Antimicrobial preservative.	Ultramarine blue and yellow iron oxide, absorb butyl paraben and thus reduce its preservative properties. [19]
		0.02–0.4	Topical preparations		
5	Carboxymethylcellulose Calcium [20]	5–15	Tablet binder	Emulsifying agent; coating agent; stabilizing agent; suspending agent; tablet and capsule disintegrant; viscosity-increasing agent; Water-absorbing agent.	Strongly acidic solutions and with the soluble salts of iron and some other metals, such as aluminum, mercury, and zinc. It is also incompatible with xanthan gum.
		1–15	Tablet disintegrant		
6	Carboxymethylcellulose Sodium [22]	0.25–1.0	Emulsifying agent	Coating agent; stabilizing agent; suspending agent; tablet and Capsule disintegrant; tablet binder; viscosity-increasing agent; water-absorbing agent.	Strongly acidic solutions and with the soluble salts of iron and some other metals, such as aluminum, mercury, and zinc. It is also incompatible with xanthan gum.
		3.0–6.0	Gel-forming agent		
		0.05–0.75	Injections		
		0.1–1.0	Oral solutions		
		1.0–6.0	Tablet binder		
7	Carrageenan [22]	*Iota 0.3–1.0	Creams, suspensions	Emulsifying agent; gel base; stabilizing agent; suspending agent; sustained-release agent; viscosity-increasing agent.	Carrageenan can react with cationic materials. Carrageenan may interact with other charged macromolecules, e.g. proteins, to give
		*Kappa 0.3–1.0	Gels		
		*Kappa 0.25–2.0	Encapsulation		

		*Iota 0.5–1.0	Creams, suspensions, lotions		various effects such as viscosity increase, gel formation, stabilization or precipitation.
		*Lambda 0.1–1.0	Creams, lotions		
8	Castor Oil, Hydrogenated [23]	5.0–20.0	Coating agent (delayed release)	Extended release agent; stiffening agent; tablet and capsule lubricant.	Most natural vegetable and animal waxes.
		5.0–10.0	Delayed release drug matrix		
		0.1–2.0	Tablet die lubricant		
9	Cellulose, Microcrystalline [24]	20–90	Adsorbent	Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.	Strong oxidizing agents.
		5–20	Anti-adherent		
		20–90	Capsule binder/diluent		
		5–15	Tablet disintegrant		
		20–90	Tablet binder/diluent		
10	Dimethicone [25]	10–30	Creams, lotions and ointments	Antifoaming agent; emollient; water-repelling agent.	-
		0.5–5.0	Oil–water emulsions		
11	Ethylcellulose [26]	10.0–20.0	Microencapsulation	Coating agent; flavoring agent; tablet binder; tablet filler; viscosity-increasing agent.	Paraffin wax and microcrystalline wax
		3.0–20.0	Sustained-release tablet coating		
		1.0–3.0	Tablet coating		
		1.0–3.0	Tablet granulation		
12	Glyceryl Palmitostearate	10.0–25.0	Matrix for sustained release	Biodegradable material; coating agent; gelling	Glyceryl palmitostearate is incompatible with

		2.0–6.0	Taste masking	agent; release-modifying agent; sustained-release agent; tablet and capsule diluent; Tablet and capsule lubricant; taste-masking agent.	ketoprofen and naproxen [27], [28].
		1.0–3.0	Tablet lubricant		
13	Guar Gum [29]	1	Emulsion stabilizer	Suspending agent; tablet binder; tablet disintegrant; viscosity-increasing agent	Acetone, ethanol (95%), tannins, strong acids, and alkalis.
		Up to 10	Tablet binder		
		Up to 2.5	Thickener for lotions and creams		
14	Hydroxypropyl Cellulose [30]	15–35	Extended release-matrix former	Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.	Substituted phenol derivatives, such as methylparaben and propylparaben.
		2–6	Tablet binder		
		5	Tablet film coating		
15	Isopropyl Palmitate [31]	0.005–0.02	Detergent	Emollient; oleaginous vehicle; skin penetrant; solvent.	Hard paraffin, strong oxidizing agents.
		0.2–0.8	Perfume		
		0.05–0.2	Soap		
		3.36	Topical aerosol spray		
		0.05–5.5	Topical creams and lotions		
16	Lecithin [32]	0.1	Aerosol inhalation	Emollient; emulsifying agent; solubilizing agent.	Esterases owing to hydrolysis.
		0.059–0.295	Biorelevant dissolution media		
		0.3–2.3	IM injection		

		0.25–10.0	Oral suspensions		
17	Methylparaben	0.065–0.25	IM, IV, SC injections	Antimicrobial preservative.	Bentonite, magnesium trisilicate, essential oils, sodium alginate, sorbitol, talc, tragacanth, and atropine [33].
		0.025–0.07	Inhalation solutions		
		0.10	Intradermal injections		
		0.033	Nasal solutions		
		0.015–0.2	Ophthalmic preparations		
		0.015–0.2	Oral solutions and suspensions		
		0.1–0.18	Rectal preparations		
		0.02–0.3	Topical preparations		
		0.1–0.18	Vaginal preparations		
18	Phenol [34]	5.0	Disinfectant	Antimicrobial preservative; disinfectant.	Albumin and gelatin.
		0.5	Injections (preservative)		
		0.5–1.0	Local anesthetic		
		41.4	Mouthwash		
19	Povidone [35]	10–25	Carrier for drugs	Disintegrant; dissolution enhancer; suspending agent; tablet binder.	The efficacy of some preservatives, e.g. thimerosal, may be adversely affected by the formation of complexes with povidone.
		Up to 5	Dispersing agent		
		2–10	Eye drops		
		Up to 5	Suspending agent		
		0.5–5	Tablet binder, tablet diluent, or coating agent		
20	Sodium Alginate	5–10	Pastes and creams	Stabilizing agent;	acridine derivatives,

	[36]	1–3	Stabilizer in emulsions	suspending agent; tablet and capsule disintegrant; tablet binder; viscosity increasing agent.	crystal violet, phenylmercuric acetate and nitrate, calcium salts, heavy metals, and ethanol in concentrations greater than 5%.
		1–5	Suspending agent		
		1–3	Tablet binder		
		2.5–10	Tablet disintegrant		
21	Sodium Bicarbonate [37]	10–40	Buffer in tablets	Alkalizing agent; therapeutic agent	ciprofloxacin, amiodarone, nicardipine, and levofloxacin (in solutions).
		25–50	Effervescent tablets		
		1.39	Isotonic injection/infusion		
22	Sodium Chloride	10–80	Capsule diluent	Tablet and capsule diluent; tonicity agent.	Aqueous sodium chloride solutions are corrosive to iron. The solubility of the antimicrobial preservative methylparaben is decreased in aqueous sodium chloride solutions and the viscosity of carbomer gels and solutions of hydroxyethyl cellulose or hydroxypropyl cellulose is reduced by the addition of sodium chloride [38].
		≤1	Controlled flocculation of suspensions		
		10–80	Direct compression tablet diluent		
		≤0.9	To produce isotonic solutions in intravenous or ophthalmic preparations		
		5–20	Water-soluble tablet lubricant		
22	Starch, Pregelatinized	5–75	Diluent (hard gelatin capsules)	Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.	-
		5–20	Tablet binder (direct compression)		

		5–10	Tablet binder (wet granulation) [39]		
		5–10	Tablet disintegrant		
23	Talc [40]	90.0–99.0	Dusting powder	Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.	Incompatible with quaternary ammonium compounds.
		1.0–10.0	Glidant and tablet lubricant		
		5.0–30.0	Tablet and capsule diluent		
24	Zinc Stearate [41]	0.5–1.5	Tablet lubricant	Tablet and capsule lubricant.	Zinc stearate is decomposed by dilute acids. It is incompatible with strong oxidizing agents.
		2.5	Water-repellent ointments		

* The carrageenans are divided into three families according to the position of sulfate groups and the presence or absence of anhydrogalactose. l-Carrageenan (lambda-carrageenan) is a non-gelling polymer containing about 35% ester sulfate by weight and no 3,6 anhydrogalactose; i-Carrageenan (iota-carrageenan) is a gelling polymer containing about 32% ester sulfate by weight and approximately 30% 3,6 anhydrogalactose. k-Carrageenan (kappa-carrageenan) is a strongly gelling polymer which has a helical tertiary structure that allows gelling. It contains 25% ester sulfate by weight and approximately 34% 3,6 anhydrogalactose.

CONCLUSION

Excipients are one of the major contributors of a pharmaceutical dosage form they may be underestimated but at times, they have had proven their usefulness. The versatility of an excipient is evident. Their uses are dependent not only on their physical or chemical traits but the concentration used, method of dosage form manufacturing also have a major role to play in determining their behavior. In reality, the functionality of the excipient can help to determine if or not a drug or a dosage form containing the drug succeeds or fails. One must look into all the possibilities before selecting excipients as some excipients are incompatible with some drugs or

other excipients. The possible consequences of selection of a non-suitable excipient for formulation may include manufacturing complications, compromised stability, poor bioavailability of the API, unintended side-effects, and even serious adverse reaction such as death of the patient.

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