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FORMULATION AND EVALUATION ASPECTS OF TABLETS-AN OVERVIEW

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ABSTRACT

Nothing in this world is stable and ever accepted. Change is the requirement of nature for the sake of adaptability. However, the pharmaceutical world is also not far off from this change. Technical advancement in pharma world also leads to the development of new dosages forms. This leads to the replacement of the older dosages forms with the newer once. But for the tablet dosages forms this replacement is substituted with modifications. On the top of it the availability of numerous evaluation parameters provides these new modifications in tablets a clear cut demonstration idea.

Keywords: Tablets, manufacturing, evaluations, analytical aspect

INTRODUCTION:

In the present scenario tablet manufacturing has cemented its place irrespective of the new advancements and technologies. With changing time requirement of rationalization and latest technologies have diverted the world market towards microsphere, nanotechnologies etc [1-6]. These advancements still continues without hampering the tablet market. New modifications are possible in case of tablets by altering the manufacturing techniques and concentration of additives. In the present world of pharma manufacturing wide variety of excipients are available

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and a lot are under research. From available additives the side effects of one is overcome by the other which provides researcher an opportunities to carry out new researches. The tablet dosage form is a versatile drug delivery system. Different types of tablet formulations are available, which is classified in Table 1. In all the cases, machinery, materials and manufacturing process remains the same with slight variations. The consistency and quality maintenance of the tablet dosage form are key challenge to all formulators.

Table 1: Different types of tablet formulations [7-20]

S. No.	Routes of Administration	Types of Tablets
1.	Oral tablets for ingestion	Multiple compressed tablets Layered tablet Modified release tablet Delayed action tablet Floating tablet
2.	Tablet used in oral cavity	Lozenges Sublingual tablet Buccal Tablet
3.	Tablet administered by other routes	Vaginal tablet Implants

Tablet Manufacturing Techniques [21-25]

Direct compression

The direct compression method is by far the most effective technique of tablet manufacturing. This technique is least tedious and hence is preferred over the other techniques. Direct compression is the simplest and most economical method for the manufacturing of tablets because it requires less processing steps than other techniques such as wet granulation and roller compaction. However, most pharmaceutical active ingredients cannot be compressed directly into tablets due to lack of flow, cohesion properties and lubrication. Therefore they must be blended with other directly compressible ingredients to manufacture satisfactory tablets.

Wet granulation

Wet granulation is a process of using a liquid binder to lightly agglomerate the powder mixture. The amount of liquid required to be properly adjusted, as over-wetting will cause the granules to be too hard and under-wetting will cause them to be too soft and friable. Aqueous solutions have the advantage of being safer to deal with solvent-based systems but may not be suitable for drugs which are degraded by hydrolysis.

Dry granulation

Dry granulation requires drugs or excipients with cohesive properties. Dry granulation is simpler than wet granulation, therefore the cost is reduced. This process is often used when the product

to be granulated is sensitive to moisture and heat. Dry granulation can be conducted on a tablet press using slugging tooling or on a roll press called a roller compactor. Dry granulation often produces a higher percentage of fine granules, which can compromise the quality or create yield problems for the tablet.

Steps-by-step tablet manufacturing processes which are being utilized by various manufacturers are enlisted in Table 2. Evaluations of these tablets are being carried out by using various response variables. Both preformulation and post formulation parameters are being evaluated to cement the effectiveness of formulated preparations.

Evaluation Parameters [26-41]

The evaluation parameters are being discussed and utilized by various researchers to evaluate various tablets formulations. There are various parameters which are studied for granules, whereas some post formulation and analytical parameters are also studied.

Pre-formulation Parameters

Angle of Repose

The angle of repose or more precisely, the critical angle of repose of a granular material is the steepest angle of descent or dip of the slope relative to the horizontal plane when material on the slope face is on the verge of sliding. This angle is in the range 0°–90°.

Bulk density and Taped density

Bulk density is not an intrinsic property of a material; it can change depending on how the material is handled. The bulk density of a powder simply expresses the amount, usually weight or mass, of a powder in a specified volume. However, since powders are composed of particles and voids, the volume occupied by a given number of particles depends on how closely they are packed. The packing of particles depends on their shape, cohesiveness, short-range motion and external forces. On practical basis bulk density of a powder tends to increase when subjected to tapping, vibration and other mechanical action which causes particles to move relative to one another in a way that allows smaller particles to occupy the voids between larger particles.

Tapped density or tapped bulk density is one formal expression of bulk density obtained under specified conditions. The "end point" used for measurement of tapped volume. Mathematically Tapped density can be defined by total number of taps (either explicitly or the product of tapping rate and time or duration of tapping) or some defined amount of small change in tapped volume from time to time, since the theoretical final volume, at infinite time/taps is approached asymptotically in an approximately logarithmic manner.

Table 2: Steps of Tablet Manufacturing Processes

Wet granulation	Milling and mixing of drugs and excipients. Preparation of binder solution. Wet massing by addition of binder solution or granulating solvent. Screening of wet mass followed by drying of the wet granules. Screening of dry granules. Blending with lubricant and disintegrant to produce "running powder" Compression of tablet
Dry granulation	Milling and mixing of drugs and excipients Compression into slugs or roll compaction Milling and screening of slugs and compacted powder Mixing with lubricant and disintegrant Compression of tablet
Direct compression	Milling and mixing of drugs and excipients Compression of tablet
Nanonization	Involves size reduction of drug to nanosize by milling the drug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated
Cotton candy process	Involves the formation of matrix of polysaccharides by simultaneous action of flash melting and spinning. This candy floss matrix is then milled and blended with active ingredients and excipients after re-crystallization and subsequently compressed to FDT.
Mass Extrusion	Involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shape of the product into even segments using heated blade to form tablets.
Sublimation	Inert solid ingredients that volatilize rapidly like urea, camphor ammonium carbonate, ammonium bicarbonate, and hexamethylenetetramine were added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials were then removed via sublimation, which generates porous structure.
Moulding	Water-soluble ingredients with a hydro alcoholic solvent is used and is molded into tablets under pressure lower than that used in conventional tablet compression.
Freeze Drying/ Lyophilization	The drug is dissolved or dispersed in an aqueous solution of a carrier. The mixture is poured into the wells of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze drying. Finally the blisters are packaged and shipped.
Disintegrant addition	Involves the addition of superdisintegrants in optimum concentration to the formulation to achieve rapid disintegration/dissolution

Carr's index

The Carr index is frequently used in pharmaceutics as an indication of the flowability of a powder. A Carr index greater than 25 is considered to be an indication of poor flowability and

below 15 of good flowability. The Carr index is an indication of the compressibility of a powder. It is calculated by the formula

$$C = 100\frac{V_B - V_T}{V_B}$$

Where V_B is the freely settled volume of a given mass of powder, and V_T is the tapped volume of the same mass of powder. It can also be expressed as

$$C = 100 \times \left(1 - \frac{\rho_B}{\rho_T}\right)$$

Where ρ_B is the freely settled bulk density of the powder, and ρ_T is the tapped bulk density of the powder.

Hausner ratio

The Hausner ratio is also used in industries as an indication of the flowability of a powder. It is calculated by the formula

$$H = \frac{\rho_T}{\rho_B}$$

Where ρ_B is the freely settled bulk density of the powder, and ρ_T is the tapped bulk density of the powder. The Hausner ratio is not an absolute property of a material; its value can vary depending on the methodology used to determine it. Use of these measures persists however, because the equipment required to perform the analysis is relatively cheap and the technique is easy to learn.

Post Formulation Parameters

Content uniformity testing

Content uniformity testing involves using a content/potency assay to determine the content of active material contained in multiple different samples collected throughout the batch. Due to increased awareness of physiological availability, the content uniformity test has been included in the monographs of all coated and uncoated tablets and all capsules intended for oral administration where the range of size of the dosage form available include 50mg or smaller sizes. Tablet monographs with a content uniformity requirement do not have weight variation requirements.

Table 3,4,5,6 represents the dissolution range, disintegration range, moisture content range, weight uniformity range and as per specified in various monographs.

Dissolution testing

Dissolution testing is used to measure the release rate of an active component from a solid dosage form under controlled conditions. This technique is used to assess the performance of tablets, capsules, films and other solids. Dissolution testing is useful in guiding the formulation development procedure and comparing finished products with different commercial preparation. Another application of dissolution testing is assessing the quality of a sample by determining the release of active pharmaceutical ingredient from the formulation is within acceptable limits.

Table 3 USP Dissolution Acceptance Criteria

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is not less than Q*+ 5%
S_2	6	Average of 12 units (S_1+S_2) is equal to or greater than Q* and no unit is less than Q*- 15%
S_3	12	Average of 24 units (S_1+S_2+S_3) is equal to or greater than Q*and not more than 2 units are less than Q*- 15%

Q*= amount of dissolved active ingredient

Disintegration test

The disintegration test is a measure of the time required under a given set of conditions for a group of tablets to disintegrate into particles which will pass through a 10 mesh screen. For a drug to be absorbed from a solid dosage form after oral administration, it must first be in solution, and the first important step toward this condition is usually the break-up of the tablet; a process known as disintegration. The IP has specified the range for disintegration of different types of tablets based on the conditions.

Table 4 Disintegration range of tablets as per monograph

S. No.	TABLETS	Disintegration Time	IMMERSION LIQUID
1.	Uncoated tablets	15mins	Water maintained at 37 ± 0.5^{O}C
2.	Coated tablets	60mins	Water at 37 ^{O}C
3.	Enteric coated tablets	2hrs	phosphate buffer pH6.8
4.	Soluble and dispersible tablets	3mins	Water maintained at 19-21 ^{O}C
5.	Orally disintegrating tablets	Less than 1 min	Petridish (10 cm diameter) was filled with 10 ml of water

*__NOTE:__ The disintegration time for ODT needs to be modified as disintegration is required without water, thus the test should mimic disintegration in salivary contents

Moisture uptake studies:

Moisture uptake studies for Fast Dissolving Tablets should be conducted to have an insight into the stability of the formulation. Ten tablets from each formulation were kept in desiccators over calcium chloride at 37°C for 24 h. The tablets were then weight and exposed to 75% RH, at

room temperature for one week. Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the desiccators for three days. Tablets were weighed and the percentage increase in weight was recorded daily.

Table 5 Moisture uptake range (ICH and FDA guide lines)

Zones	Mean Kinetic Temperature (°C)	% RH (yearly)
Zone I (Moderate)	21	45
Zone II (Mediterranean)	25	60
Zone III (hot, dry)	30	35
Zone IV (very hot, moist)	30	70

Uniformity of weight:

20 Tablets of all the batches were collected randomly during compression and weight of individual tablet was carried out. Limit: Weight of all individual tablets should be in the limit of Average wt ± 7.5%. Average weight was carried out by calculating the total wt. of 20 tablets (individually weighed) and dividing this value by 20.

Table 6 Weight Variation Tolerance for Uncoated Tablets

Average Weight of Tablets (mg)	Maximum % Difference Allowed
130 or less	10
130-324	7.5
More than 324	5

ANALYTICAL PARAMETERS [42-50]

Many researchers have also evaluated this oral dosages formulation using different analytical techniques. RP-HPLC, HPLC, UV-VIS spectrophotometry etc is being utilized for this purpose and produces extremely valuable results. El-Arini et al.[51] carried out the evaluation of disintegration testing of different fast dissolving tablets using texture analyzer. Wilson et al.[52] studied the behavior of a fast-dissolving expidet followed by gscintigraphy. Washington et al.[53] utilizes gamma scintigraphic technique to study of gastric coating by expidet tablet and liquid formulations. Brampton et al.[54] carried out double-blind crossover study of the efficacy and acceptability of oxazepam expidet tablets compared to placebo in patients undergoing gynaecological surgery. Morita et al.[55] evaluated the disintegration time of rapidly disintegrating tablets by novel method utilizing a CCD camera. Ali et al [56] utilized near-infrared spectroscopy for nondestructive evaluation of tablets. Jedvert et al.[57] evaluated the active ingredient in tablets by NIR and Raman spectroscopy. Meza et al. [58] carried out quantitation of drug content in a low dosage formulation by transmission near infrared spectroscopy. Romer et al.[59] devised a method

for prediction of tablet film-coating thickness using a rotating plate coating system and NIR spectroscopy. Perez-Ramos et al.[60] make the quantitative analysis of film coating in a pan coater based on in-line sensor measurements possible. These advance techniques are proven boon to the pharmaceutical sciences and life sciences. The demerits of post formulation and pre formulation parameters can be easily resolved using these technological developments. However these techniques prove costly, but its time saving benefit overpowers the economical aspects.

CONCLUSION

Tablet manufacturing and its evaluation has become the backbone of pharmaceutical research. From the various data sources it could be concluded that tablets have got uniqueness and power of adaptability. The tablets have shown vast changes in the last few decades or so both in manufacturing and evaluation. The advances in the evaluation techniques have proven to be both economical and time saving. From the number of manufacturing and evaluation parameters available the scope for the researchers also enhances and makes it possible for tablets to perfectly cement its place in this ever changing drug world.

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