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A Review on Multiple Compressed Tablets

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ABSTRACT:

Multiple compressed tablets are compressed tablets made by more than one compression cycle. They are usually prepared to separate physically or chemically incompatible ingredients or to produce repeat or prolong action of drug. Compression coating perform similar functions as sugar or film coating except consists of dry coating concept hence prevents certain drawbacks of aqueous and non aqueous solvents used in sugar and film coating. There are three categories under this class: Compression coated tablets, Inlay tablets and Layered tablets. Multiple compression tablets, especially layered tablets, tend to solve incompatibility issues between two or more active pharmaceutical ingredients (APIs). Bilayer tablet provides adequate surface separation of two reactive ingredients but there may be some reactivity at the interface. If complete physical separation is required for stability purposes then three layered tablet may be employed.

Key words: dry coating, layered tablet, Inlay tablet, Incompatibilities.

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INTRODUCTION:

Despite the ongoing development of more sophisticated solid drug delivery systems, tablets are still by far the most prevalent solid dosage form. Not all active pharmaceutical ingredients (API) inherit favorable physicochemical characteristics for production, storage and administration, thus requiring dosage form modifications such as coating. Coating can improve taste, aesthetic appearance or mask odor. In addition to this, tablets are often coated with a therapeutic purpose. For example, enteric coating is used to protect the API against degradation in the stomach and sustained release coating is used to obtain a desirable API absorption rate, and hence an optimum plasma-release profile[1].

Although the pharmaceutical industry has a long history of sugar coating, now a day's film coating is widely accepted due to its various advantages. In film coating, there are many organic solvents used but it requires large quantities of organic solvents and thus gives rise to the disadvantages of economy, safety and environmental pollution. In film coating if water is used in place of organic solvent then it creates various problems, such as aqueous dispersion is unstable to some physical changes. The above problems can be overcome by the compression coated tablets consists of dry coating concept. It also functions like sugar-coated or film-coated tablets [2].

MULTIPLE COMPRESSED TABLETS:

Multiple compressed tablets are prepared by more than one compression cycle. This process is best suited when separation of active ingredient is

needed for stability purposes, or if the mixing process is inadequate to guarantee uniform distribution of two or more active ingredients [3, 4]. They are also known as multiple layered tablets or a tablet within the tablet. There are three categories under this class: Compression coated tablets, Layered tablets and Inlay tablets.

COMPRESSION COATED TABLETS:

Compression coated tablet has two parts, the first part is internal core and the second part is surrounding coat (fig.1) [5].

Rationale of compression coated tablets:

This tablet readily lends itself into a repeat action. Outer layer provides the initial dose while the inner core releases the drug later on. Hence, it is useful for releases of two active pharmaceutical ingredients (APIs), one immediate release formulation which is entrapped in coat and the other sustained release formulation entrapped in the core. It is also possible to provide loading dose and maintenance dose for one drug using this concept. Sometimes, inner core may consist of liquid formulation to provide immediate release of core after the coat gets dissolved. Amrutkar *et al.* prepared bilayer tablet formulation of metformin hydrochloride and gliclazide for diabetes treatment. Sustained release layer of metformin hydrochloride was prepared using hydrogenated castor oil and HPMC K100 M polymers and immediate layer of gliclazide was optimized separately. They proved that bilayer tablet is the most suitable drug delivery system for fixed dose combination [6]. Compression coated tablets with a lag time before drug release is a potentially useful formulation for chronopharmacotherapy. It can control the time and duration of plasma drug concentration better than existing sustained release technologies. Sawada *et al.* prepared compression coated time release tablets (CC tablets) containing nifedipine where each formulation showed a clear lag period before nifedipine release initiation, followed by sustained drug release lasting up to 24 hours[7].

Compresssion coated tablets can also provide delayed released action of drug. Baojian *et al.* performed hydrogel compression coated tablets to release 5-fluorouracil from hydroxypropylmethycellulose (HPMC) coated tablet. Drug release was delayed initially due to hydrogel swelling/retarding effect, followed by zero-order release [8]. Yehia *et al.* formulated budesonide (BUD) compression coated tablets for colonic specific delivery. Pectin and guar gum were used as enzyme dependent polymers[9].

It solves the incompatibility issues by keeping two APIs separate; one drug is present in internal core and second is embedded in surrounded coat. Friedl *et al.* solved incompatibility issues between telmisartan and hydrochlorothiazide using this technique[10].

It can protect active pharmaceutical ingredient from acidic environment of stomach by utilizing buffering concept. For example compression coated tablet having sodium salicylate & sodium bicarbonate present in core and coat respectively. After oral administration, sodium salicylate converts into salicylic acid in the presence of gastric hydrochloric acid and leads to precipitation. Therefore coat the tablet with sodium bicarbonate which neutralizes the hydrochloric acid presents in stomach and prevent conversion of sodium salicylate to salicylic acid.

Manufacturing of compression coated tablets:

The core is small porous tablet and prepared on one turret. For preparing final tablet, a bigger die cavity in another turret is used in which first the coat granules are filled to half and core tablet is mechanically transferred, again the remaining space is filled with coat material and compression force is applied (fig.2) [2, 11- 13]. Core tablets are prepared by wet granulation method or direct compression method as the conventional tablets. Coating granules can be prepared by using drug and excipients as per desired action of tablet. Some of the excipients are enlisted in Table 1.

Equipments used to prepare compression coated tablets:

Colton 232, Stock 538 and Manesty Drycota 900 are equipments utilized for preparing compression coated tablets. Two of them provide separate machine for coating whereas one provides compression of the core on one side of the machine with almost instantaneous transfer of core to other side for coating. In Table 2 comparison among three compression machines are mentioned.

Critical Parameters need to be considered during formulation development:

Cohesiveness: Coating granulation requires excellent cohesiveness as well as the ability to adhere tightly to the

core. Poor cohesiveness leads to capping or lamination. The amount of glidants, disintegrants and lubricants should be not more than 10% of the batch, since these are powders with little cohesiveness. Coating material should not have more amount of fine to avoid poor cohesiveness.

Plasticity: Coat granulation should be plastic enough to expand slightly with the slight swelling of the core after the extrusion of the completed tablet from the die. Insufficient plasticity of core tablet leads to sticking of core tablet to coat layer. Because the edges of compression coated tablets are thicker than those of ordinary tablets, larger amount of lubricant is needed to facilitate extrusion from the die.

*Softness of granule*s: The granules should be relatively soft. Hardness of tablet increases due to hard granules and it may affect the disintegration time and dissolution profile of tablets. It can be overcome by adding materials which tend to hold water like lactose. Material which produces hard granules like sucrose should be avoided.

Improper centration of the core: Improper centration of the core vertically or horizontally produces a weak edge (fig.3) and cannot hold coating together. Poor centration may be due to the poor flow of granules[14]. Fine granules cause the least movement of the cores[15].

Temperature: Waxes are used for sustained release products. Above 75°F temperature, wax core may soften and cause sticking in the transfer cups or V-slots. Careful selection and control of temperature is essential during formulation and storage of dosage from.

Advantages of compression coated tablets:

The chief advantage is the elimination of water or other solvent in the coating procedure. Thus there is no need for a barrier coating to prevent water from penetrating the cores and possibly softening them or initiating an undesired reaction. If a drug tends to discolor readily or develop a mottled appearance because of oxidation or sunlight, incorporating the drug in the core tablet can minimize these problems. It may cover a bitter substance, conceal an unpleasant or mottled appearance, or provide a barrier for a substance irritating to the stomach or one inactivated by gastric juice. Immediate release portion is compressed around a slowly releasing core which provides accurate dose compare to simple matrix tablet[2].

Disadvantages of compression coated tablets:

The compression coating technique is rarely employed in the industry. It has not yet replaced film coating due to simple and inexpensive nature of film coating. Larger quantities of tablets can be coated in a short time by film coating. Recent advances in coating equipment, such as the side vented pans, have increased the efficiency of the aqueous coating operation to a point where even aspirin tablets may be aqueous coated without significant hydrolysis. This has greatly increased the popularity of film coating over compression coating[2].

Compression coated tablets produce significant increase in size and weight of the core tablets compared to film coated tablets. The immediate release portion must be applied in increments; the cores do not pick up weight equally, those with increased surface area gain at the expense of those with less. Thus at the end of a coating run, tablet weights and drug content may vary as much as ±20% for individual tablets, depending on the number of coats required[2].

LAYERED TABLETS:

Layered tablets are composed of two or three layers of granulation compressed together. They have the appearance of a sandwich because the edges of each layer are exposed. When two or more active pharmaceutical ingredients are needed to be administered simultaneously and they are incompatible, the best option for the formulation pharmacist would be to formulate multilayered tablet. A single tablet composed of two or more layers and usually each layer is of different color to produce a distinctive looking tablet [1,16,17].

There are mainly two type of layered tablets used in pharmaceutical industries: Bilayer tablet and Trilayer tablet.

Rationale for bilayer tablet:

In bilayer tablet release of both drugs start immediately compare to compression coated tablet where first drug releases from coat followed by drug releases from core. It solves incompatibility issues between two or more active pharmaceutical ingredients by providing limited contact. Khedkar *et al.* [11] solved

incomaptibilty between amodiaquine hydrochloride and artesunate using this technique.

Modified drug release can be achieved by preparing bilayer tablets. Kulkarni *et al.* proved that floating bilayer tablet was effective to deliver more than one drug for better patient compliance and disease management. They had designed floating bilayer tablets of sustained release diltiazem hydrochloride and immediate release lovastatin [18]. Narendra *et al.* formulated bilayer gastric floating tablet containing metoprolol tartrate as a model drug for gastric retention [19]. Nasra *et al.* developed the metronidazole colon-specific multilayer tablets using pectin as a carrier [20]. Miyazaki *et al.* designed and evaluated both single and bilayer tablets of pectin and HPMC in the ratio of 1:1 for the sublingual delivery of diltiazem. Bilayer tablet showed more prolonged release pattern compare to single layer tablet [21].

It is possible to do dose adjustment by splitting of bilayer tablets. Numerous antihypertensive drugs require dose adjustment where tablet splitting technique can be used. Barry *et al.* prepared ACCU-B types of ACCU-BREAK tablet technology where they used an inactive layer (segment) as the break region. In bilayer (ACCU-B) tablets, the layer containing drug can be scored into 2, 3 or 4 equal segments, all adjacent to an inactive breakable support segment. Thus, a tablet could be broken easily into the specific dose desired. For example, a 10 mg quadrisected ACCU-B amlodipine tablet could permit the initial dose to be 2.5 or 5 mg (¼ or ½ tablet) with dosage adjustments as needed using the same prescription. These tablets are shaped and sized so that they can be readily broken by hand or swallowed whole. The inactive segment does not affect drug release kinetics [22,23].

Manufacturing of bilayer tablets:

Layered tablets can be produced by adding multiple granulations to the die cavity with multiple compaction steps between each addition followed by a final compression or compaction [24]. In the operation, the granulation for the first layer is placed in the hopper, and the machine is adjusted until the desired weight is achieved with consistency, then the second hopper is filled with its granulation, and the same procedure is followed until the correct total tablet weight is obtained. In single compression method, the delineation between layers tends to be a little uneven. It is also difficult to make weight adjustments during a run.

Of the modern age there are two types of machines are available in market. In one, the first layer of the first two layers are diverted from the machine; in the other, the first layer is made so hard that the second layer will not bond to it or will bond only weakly; upon ejection of the completed tablet, the layers may be easily separated and tested individually. It is not necessary that each layer should have the same thickness. The shape of the punches also plays a role: punches with beveled edges or concave faces make thin top and bottom layers of a three-layer tablet compare to middle layer. Each layer is fed from separate feed frame with individual weight control. Therefore, each layer undergoes light compression as each component is laid down. This avoids granules intermixing if the machine vibrates [1,25-27]. Dust extraction is essential during compression to avoid contamination. Comparison of bilayer compression machines with Single rotary compression Machines, Double rotary compression machine are shown in fig.4.

Rationale for trilayer tablets:

Bilayer tablets have only one interphase between two drug layers so incompatibility between two drugs may occur at this point. Trilayer tablets can solve this kind of interphase incompatibility problem between two drugs (fig.5). In trilayer tablet two or three drug releases simultaneously [11].

Manufacturing of trilayer tablets:

Manufacturing of trilayer tablet is as similar as bilayer tablet only in addition, it involves third hopper to incorporate polymer (inert) blend or third active pharmaceutical ingredient's granules.

Equipments used to prepare layered tablet:

Various compression machines used to prepare layered tablets with their specifications are mentioned in Table 3.

Critical Parameters need to be considered during formulation development:

Effect of dust on hardness: Fines should be kept to a minimum. It may be necessary to separate out that fraction of granulation, which is finer than 70 or 80 meshes. Such material is not discarded but added to the

next lot and regranulated. Lubricants, however, must be finely divided as their efficiency depends on the degree of fineness. Since these lubricant fines cannot be avoided, the quantities used should be kept minimal. The metallic stearates present an additional difficulty in that they interfere with the bonding of the layers. Stearic acid and the hydrogenated fats are better lubricants from this point of view [1].

Effect of Moisture: Moisture Content should be less than 1% w/w. Control of moisture content, improves compaction properties.

Effect of Hardness: More hardness may cause either layers separation or decrease in solubility or dissolution[11].

Advantages of Layered tablets:

Multilayered tablets are mainly used for incompatible substances [28]. Layered tablet makes possible sustained release preparations with the immediate release quantity in one layer and the slow release portion in the second. A third layer with an intermediate release might be added. In layered tablet the weight of each layer can be accurately controlled, in contrast to putting one drug of a combination product in a sugar coating. Monograms and other distinctive markings may be impressed on the surfaces of the multilayer tablets. Coloring the separate layers provides many possibilities for unique tablet identity. Analytical work may be simplified by a separation of the layers prior to assay. Since there is no transfer to a second set of punches and dies, as with the dry coating machine, odd shapes (such as triangles, squares, and ovals) present no operating problems except for those common tooling.

Bilayer tablets require fewer materials than compression coated tablets and hence contain less weight and may be thinner as compared to compression coated tablets. Manufacturing of bilayer tablet is easy.

Disadvantages of layered tablets:

Layered tablet tend to be more expensive to manufacture than other tablets because of requirements of multiple granulation steps and some presses work at lower speed. Chances of cross contamination are high due to usage of multiple drugs. In bilayer tablet there is one inter phase between two drug layers so there are chances of interaction at one phase. Certain parameters like hardness and thickness need to be check for each layer.

Marketed products:

Many pharmaceutical industries have tried concept of layered tablets to achieve any of the above mentioned rationale. Some examples include CLARINEX-D(R) (desloratadine 2.5 mg /pseudoephedrine 120 mg) [29], Coma Arthritis Pain Reliever by Sandoz consumer [30]. Torrent R & D is working on Multiple Layer Matrix Systems of Isosorbide 5-mononitrate SR + Aspirin and Alprazolam SR + Sertraline HCl [31].

INLAY TABLETS:

A variation of the compression coated tablet is the inlay, dot, or bull's-eye tablet. Instead of the core tablet being completely surrounded by the coating, its top surface is completely exposed. With a yellow core and a white coating, the tablet resembles a fried egg (fig.6).

Rationale of Inlay tablets:

This form can be useful in sustained release preparations to reduce the size and weight of the tablet. Two drugs are incorporated in tablet, one in core and one in coat. Release of both drugs starts immediately but coating is responsible for slow release and core is responsible for immediate release of incorporated drugs. Example is a European preparation containing 25 mg of hydrochlorothiazide in the bull's-eye and 600 mg of potassium chloride in the outside portion. The latter contains a waxy substance to retard release and obviate gastrointestinal irritation. Thus the inlay is available immediately for its diuretic activity. To surround the potassium chloride with a granulation containing the hydrochlorothiazide would result in a tablet at least 1/2 in. in diameter and in a great waste of materials [2]. This concept is also applicable for combination of Metformin (500 mg) and Pioglitazone (15 mg) combination tablet as well as immediate release Rosiglitazone and sustained release combination tablet [31].

Manufacturing of Inlay tablets:

The preparation of inlay tablet is as like compression coated tablet but in inlay tablet the top layer of coating is eliminated. Only the bottom layer of coating is deposited in the die. The compression wheels embed the core tablet in the granulation, displacing

some of to form the sides. It also displaces some coating granules to form sides. And finally press the whole into a tablet.

Inlay tablet are prepared with the Stokes, Colton, or Kilian machines. No alterations in equipment are needed only the feed frame and hopper, which normally provide the top coating, are not installed. The Manesty DryCota, which utilizes a two compartment feed frame for coating so it is necessary to block off the second part so that the granulation is diverted away from the dies and around the turret.

Advantages of Inlay tablets:

It requires less coating material, only about 25 to 30% more than the weight of the core. The reduction in the amount of coating makes a thinner tablet. The core is visible, so coreless tablets are readily detected. There is (of course) no concern with the capping of the top coating. It is a new platform technology for decreasing the mechanical shear on double compressed products which can lead to decrease in unknown process related impurities. Inlay tablets can be useful in sustained release preparations to reduce the size and weight of the tablet.

Disadvantages of Inlay tablets:

Inlay tablets attain less hardness, which leads to high friability so more care need to be taken during transportation and storage [2].

CONCLUSION:

Multiple compression tablets are classified as compression coated tablets, layered tablets and Inlay tablets. Compression coated tablets involves concept of dry coating which overcomes problems associated with tradition film or sugar coating. It can modify drug release pattern by using suitable excipients in core and coat. Layered tablets are preferred by industry to solve incompatibility issues between two or more drugs. Problem associated with majority of sustained release tablets is that they increase in size and weight of dosage form which can be overcome by inlay tablets.

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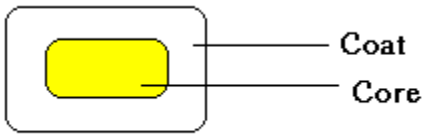


Fig.1: cross sectional view of compression coated tablet

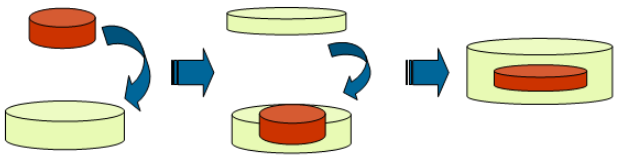


Fig.2: Manufacturing process of compression coated tablet

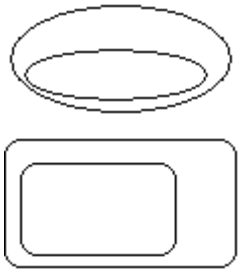
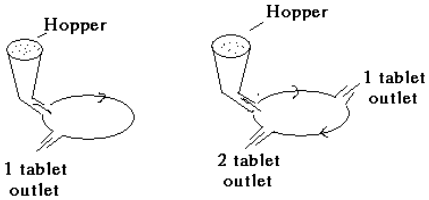
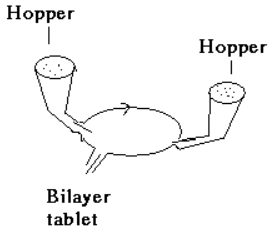


Fig.3: off center coating



Single rotary compression Double rotary compression



Bilayer compression

Fig.4: Comparison of single rotary, double rotary and bilayer compression machine

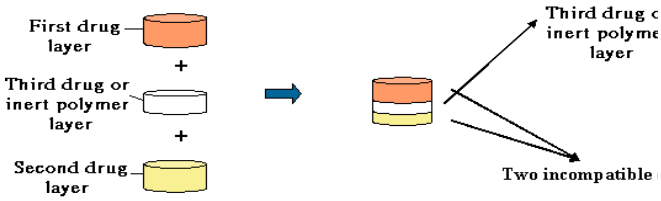


Fig.5: Trilayer Tablets

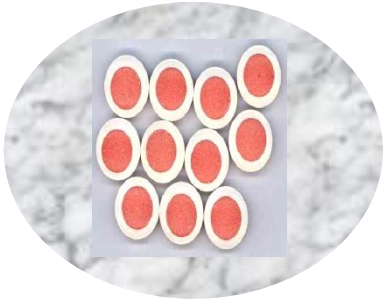


Fig.6: Diagram of inlay tablet

TABLE 1: CHOICE OF INGREDIENTS IN COATING GRANULES PREPARATION

=Category	Ingredients
Medicament	As per formulation
Plasticizers	Gelatin, polyethylene glycol 6000
Lubricants	Magnesium stearate, polyethylene glycol 6000
Binders	Sucrose, Starch NF, Gelatin NF, Acacia NF
Polymers	Ethyl cellulose, Hydroxy propyl methyl cellulose, Povidone, Eudragit & RS, Polyethylene glycol

TABLE 2: SPECIFICATIONS OF COMPRESSION MACHINES USED FOR COMPRESSION COATED TABLETS

	Manufacturer and model designations			
	Colton 232	**Stock 538**	**Manesty drycota 900**	**Core coating**
Maximum tablet diameter (in.)	5/8	5/8	9/16	5/8
Maximum depth of fill (in.)	½	11/16	-	7/16
Number of compression stations	33	27	23	23
Maximum output (tablets per min)	900	500	950	900
Pressure (tons in.-2)	3	4	6	6

TABLE 3: SPECIFICATIONS OF COMPRESSION MACHINES USED FOR LAYERED TABLETS

Specification	Manufacturer and model designation						
	Manset y Layerpr ess	Manesty Rotapress mk IIa	Killian RU -3S	Stockes Versapress 560 - 1	Fette P - 3002	Hata HT AP55L-DU	Vector Magna
Number of dies	47	61	20	45	55	55	90
Maximum Pressure (tons)	6.5	6.5	8.5	4	20(kN)	9	10
Maximum tablet diameter (in.)	7/16	7/16	3/4	7/16	1/2	1/2	7/16
Maximum depth of fill (in.)	11/16	11/16	9.16	11/16	5/16	5/16	___
Maximum layer thickness(pior to pressing) (in.)							
First layer							
Second layer	1/4	7/16	1/4	7/16	11/16	___	3/4
Third layer	1/4	1/4	1/4	1/4	11/16	___	3/4
	1/4	___	1/4	___	___	___	3/4
Maximum output (TPM)	1,500	5,550	417	2,100	4,125	3,850	5,000