REVIEW ARTICLE

Tablet in Tablet - An Innovative and Pragmatic Approach in Tableting Technology

Kapil Kanwar[1]*, Surya Prakash Gautam[2]

[1]Department of Pharmacy, I. K. Gujral Punjab Technical University, Kapurthala, Punjab, India, [2]Department of Pharmaceutical Sciences, CT Institute of Pharmaceutical Sciences, Jalandhar, Punjab, India

Abstract

Tablets are the most widely used formulation amidst all dosage forms as its convenient to intake, offer precise dosing and, have low cost. Functionally, compressed tablets can be categorized into simply compressed tablets, coated and multiple compressed tablets. Further, multiple compressed tablets can be classified as layered tablets and tablet in tablet dosage form. Among these, tablet in tablet technology is an innovative and pragmatic approach, where a tablet is compressed with a core tablet in the center. Moreover, the inlay tablet is also a form of tablet in tablet where the top surface of the core tablet is completely exposed within the outer tablet. tablet in tablet technology offers various advantages over conventionally coated tablet formulations. There is, no water penetration into the core tablet hence, no core softening occurs, no seal coat is required over the core tablet. Incompatible API's can be formulated into a single tablet by physically separating them. Drug deterioration can be curtailed down by incorporating sensitive API into a core tablet, thus preventing environmental degradation. It also prevents drug degradation in the gastric environment, helpful in concealing the bitter and unpleasant taste of the drug, despite this, the technology has some minor disadvantages like improper centration which may cause fragile edges, and low-density drug substances in the core may lead to inappropriate formulation size. There are certain considerations to be taken while developing formulation in tablet in tablet dosage form. Ideally, the weight of outer tablet granules must be kept twice in weight to that of a core tablet. The core tablet must be kept as small as possible. The outer tablet granules must possess cohesiveness and plasticity to produce a physically stable formulation. There are various Machines available to manufacture tablet in tablet formulation, namely, the Colton Model 232 and the Strokes model 538, Manesty Drycota, etc. There are many formulations developed as well as approved patents using tablet in tablet technology whereby it replaces conventional coating techniques, overcoming incompatibility, and stability issues. This review is an attempt to congregate and present meaningful insight to this revolutionary technology.

Keywords: Multiple compressed tablets, Layered tablets, Tablet in tablet, Compression coated tablet, One-step dry coating, Inlay tablets

INTRODUCTION

Tablets are solid unit dosage form, primed by compaction of formulation constituents containing medicament/ medicaments, with suitable excipients. It is the most extensively used formulation; among all dosage forms. They are portable, convenient and easy to use/administer. Tablet formulation offers precise dose, high degree of dosing accuracy and are comparatively inexpensive than other types of oral formulations. The functionality of tablet formulation is determined by its design.[1] Based on functionality, compressed tablet formulation can be classified as simply compressed tablets, coated tablets, and multiple compressed tablets.

Simply compressed tablet are uncoated tablets that offers immediate drug release, whereas coating is done to generally convex shaped compressed tablets for diverse advantages, it offers over uncoated tablets, namely, film coating (protection from environmental degrading factors, i.e., humidity, oxygen, and light), enteric coating (delayed action tablet formulation, prevent disintegration of tablet in stomach thus

Address for correspondence:
Kapil Kanwar, Department of Pharmacy, I. K. Gujral Punjab Technical University, Kapurthala - 144 603, Punjab, India. E-mail: kanwarkapil@gmail.com

Received: 21-04-2022
Revised: 24-05-2022
Accepted: 30-06-2022

prevent degradation of acid labile drugs), and sugar coating (taste/odor masking, sustained action). Coating is done with amalgamation of various polymers to offer diverse coating characteristics to produce control release/repeat action/ extended release tablet formulation.

Multiple compressed tablets are formulated after two to three compression cycles. These are formulated to keep incompatible APIs separately in same tablet, to make sustained or dual-release products.[1] Multiple compressed tablets are further categorized as layered tablets [Figures 1 and 2][2,3] and tablet in tablet. As the name suggest, in layer tablets, two to three layers of different granules are compressed together. It gives them, a sandwich like appearance because of its exposed boundaries,[4] where as in tablet in tablet [Figure 3];[5] the core tablet is completely enclosed in the outer tablet. It is also expressed as compression coated tablet where outer tablet plays the role of coating over the core tablet.[1] Tablet in tablet is an innovative and pragmatic approach, where a tablet is compressed with a core tablet in the center.[6] Inlay tablet [Figure 4][7] is also a form of tablet in tablet with the difference that the top surface of core tablet is completely exposed in inlay tablets.[4] Inlay tablets are also termed by some researchers as core in cup tabs, exposed core tablets, bull's eye tabs.

HISTORY AND PATENTS

The concept of tablet in tablet is not new. Different researchers used different terms, namely, one-step dry coating (OSDrC), Press coated tablet, Compression coated tablet, single/bilayer core-containing tablets, compression-embedding technique, dry coating, etc., to categorize this concept. concept dates back to 1896, a British Patent was granted for a rotary compression machine, capable to execute tablet in tablet. This rotary compression machine consist of three hoppers; two hoppers deliver granules for the upper and bottom layer, third hopper supplies previously compressed core tablet through reciprocating finger into the die. This machine was also capable to provide excellent centering to the core tablet.[4]

In 1917 US Patent was also granted for a tablet compression machine that was capable to introduce previously compressed core tablet into a die through toothed disk. This patent specifies his compression machine as layer press but it was also capable to produce tablet in tablet, if core was smaller than the diameter of the die.[4]

The DeLong Gum Company of Massachusetts acquires a British patent in 1935, for their compression machine which was capable to compress sugar composition on previously prepared biconvex chewing gum cores. Impeccable centration was attained by concave punches, convex cores, lubricity of coating and finger like device that aids in insertion of the cores.[4]

Figure 1: Bi-layer tablets[2]

Figure 2: Tri-layered tablets[3]

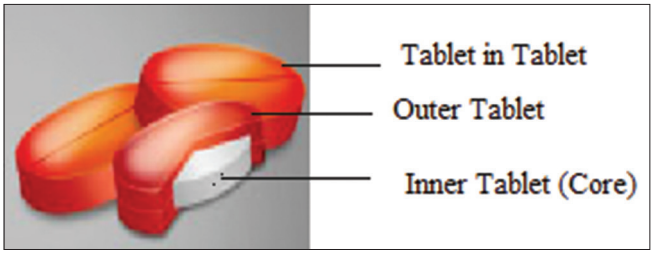

Figure 3: Tablet in tablet[5]

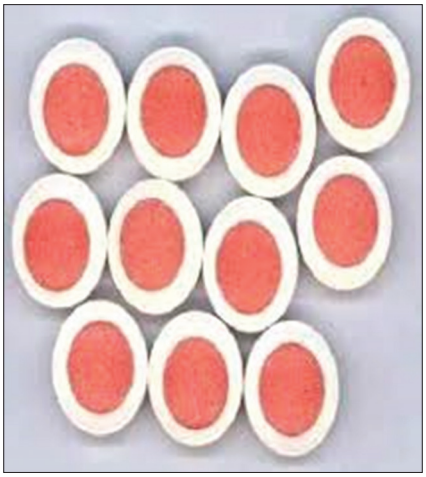

Figure 4: Inlay tablets[7]

A German inventor Kilian received a British patent in 1937, for his tableting machine, which was not only capable to compress core but also coat them; on a single machine. It contained specially designed upper punch that contained Punch rod which passes lengthwise through them. These upper punches hold the core tablet after compression, there after these upper punches passes over by a roller which presses down punch rod and ejecting the core onto transfer plate which further carries them to coating machine. Kilian, in association with Evans Medical Supplies, Ltd., invent

Prescoter in which core tablets were introduced on to feed plate through vibrating hopper. The feed plate introduces core in to the dies for compression of outer tablet. Coreless tablets were located by rejection device which senses variation in hardness of tablet with core and tablets without core.[4]

In 1967, Edward Alexander Hotko, Scotch Plains and Leon Lachman acquired US patent (3325365) for developing process of applying enteric coating to core tablets by compression. This process was better than traditional method of coating by pan, resulting in uniform and controlled weight of coating with minimal inter and intra batch variation.[8]

In 1985, Groenendaal and Sijbrands bagged European patent (0181650) for the process of compression coated dispersible tablets. According to the patent, his formulation consist of active drug substance in quickly dispersible core tablet which was surrounded by outer coat, compressed around core; of quickly dispersible constituents, which forms a readily drinkable mixture when dispersed in water.[9]

In 2002, Sawada *et al*., acquired US Patent (US 2002/0028240A1) on Timed-release compression-coated Solid composition for oral Administration. Their patent consists of formulation, with API in core tablet and outer layer consist of hydrogel forming polymer along with hydrophilic base.[10]

In 2002, Ting and Hsiao got US Patent (US 2002/0164371 A1) for press coated, pulsatile drug delivery system suitable for oral administration. Their formulation consists of immediate release compartment (compressed blend of API in outer tablet containing hydrophilic polymer) and extended release compartment (core tablet containing API along with hydrophobic polymer).[11]

In 2003, Hariharan and Gupta, Hariharan *et al*. received US Patent (US 2003/0091625 A1) for developing various methods and device for manufacturing compression coated tablets. Their technique consists of unique upper punch which was having hollow shaft. In this hollow shaft resides Punch rod whose tip could be extended or retracted as punch rod moves with in hollow shaft. Alternative way was also established and described in which two different types of solid upper punches were used. These were punches with extended tip and retracted tip. The punch with extended tip was used to produce cup shaped compact, which forms a part of outer tablet [Figure 5][12] and punch with retracted tip was used to produce tablet in tablet (compression coated tablet) after placing core in cup shaped compact in die followed by placing more of outer tablet material and compression with retracted punch.[13]

In 2006, Guo *et al*. acquired US Patent (US 2006/0193915 A1) for their pharmaceutical formulation meant to administered orally comprising bitter and nasty drug substance. They consider 3-2-(dimethy lamino) ethyl-N-methyl-1H-indole-5-methanesulphonamide (Sumatriptan) in core tablet which was used for treatment of cephalic pain. This core tablet was compression coated with non-interacting material to eliminate API's bitter taste and unpleasant smell.[14]

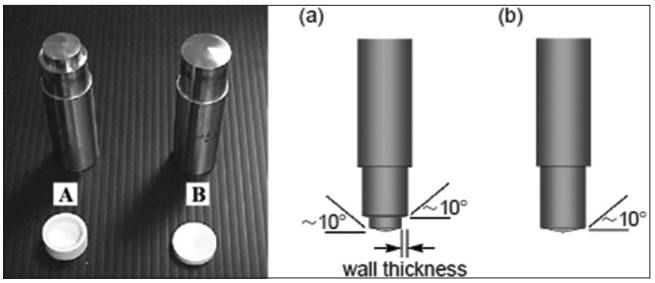

Figure 5: (a) Upper punch used to make Cup. (b) Punch for final compression[12]

In 2007, Judy and Persicaner acquired US Patent (US 2007/0160670 A1) for process containing Compression-coated tablets and manufacture thereof. There formulation contains Sumatriptan in core tablet (used in treatment of migraine); outer tablet, that is, mantle is free from active drug substance which is positioned to mask the unpleasant taste of Sumatriptan.[15]

In 2007, Doshi *et al*., received US patent (US 2007/0275067 A1) for their pharmaceutical composition intended for oral administration, containing pharmaceutically active material in core of tablet and outer tablet was compressed around core with non-active composition which was designed to enhance the taste and palatability of formulation containing unpleasant tasting active drug in core.[16]

In 2013, Nutalapati and Lad acquired US patent (US 2013/0064889 A1) for tablet-in-tablet of paliperidone formulations and methods for production and use thereof. They had prepared the control release formulation containing paliperidone in core and compression coating outer tablet also containing paliperidone, to form a tablet-in-tablet control release formulation.[17]

In 2015, Grenier *et al*. received US patent (US 8980363 B2) for developing method and apparatus for producing a centered compression coated tablet. They had developed a technique for positioning core in the center of tablet in tablet. Their innovation was based on tooling which can be used with little modification on tablet press intended for compression coating. Their invention uphold core in the center after initial deposition of bottom fill and limit centrifugal force that may cause off centering on high speed press.[18]

Kawano *et al*. bagged US patent (US 9433632 B2) in 2016 for their invention comprising tablet in tablet. A patent constitutes a dry coated tablet; with enteric coated acetyl salicylic acid in inner core and enteric coated micro granules containing proton pump inhibitor in outer layer. Their

formulation expressed enhanced physical stability and superior pharmacological effects.[19]

MERITS AND DEMERITS OF TABLET IN TABLET TECHNOLOGY

Merits

1. The tablet in tablet technology is also expressed as compression coating technology. The key benefit of this technology is, exclusion of water/solvent during coating, thus in this technique, there is not any penetration of water into the core tablet hence No core softening or initiation of undesirable chemical reaction takes place.[4]
2. No seal coat or barrier coat over the core tablet is required consequently there isn't any delay in disintegration and dissolution of core tablet, that is, there in case of pan coating.[4]
3. Core tablet is coated by compression in single step thus eliminating various time consuming steps (diverse alternative steps of coating and drying) followed during pan coating.[4]
4. Incompatible API's can be formulated into single tablet by physically separating them by placing one API in core and other API in coating (outer tablet).[4]
5. Certain drug components are prone to deterioration because of exposure to light, air or humidity such complication can be curtailed down by incorporating such drug component into core tablet.[4] No additional coating is required to protect the drug from adverse environmental conditions.
6. Tablet in tablet technology prevents drug degradation in gastric environment. Drug degradation at lower pH in stomach can be prevented by placing such acid labile drug in core tablet.[4]
7. Certain drugs like NSAIDs (Nonsteroidal anti-inflammatory drugs) cause gastric irritation leading to complications such as nausea, vomiting, heart burn, and gastric ulcer. Such drug induced conditions can be avoided by placing such drug components in core tablet thus outer tablet will act as barrier evading direct interaction of irritant drug with stomach.[4]
8. This technique is helpful in concealing bitter and unpleasant taste/nauseating odor of drug by placing it in core tablet.[4] It also eradicates discoloration and enhances stability of active ingredients present in core.[20]
9. No such coating defect are observed with compression coated tablets as seen in pan coating, namely, orange peel, blistering bridging/filling, cracking, and picking sticking.
10. Weight variation and drug content variation are observed in sustain release tablet formulation prepared by pan coating technique depending on number of coating cycles but such variation is negligible with sustain release tablet formulation prepared by compression coating technique (Tablet in Tablet Technology) as the weight of outer tablet is twice or more, to the weight of core tablet to form uniform covering over core tablet.[4]
11. Tablet in tablet technology is conventionally used to manufacture Sustained release, control release, and delayed release tablet formulation. In certain cases it can be used as immediate release formulation, in which drug components in core and outer tablet may act in synergy to produce desired pharmacological action or outer tablet only act as barrier coating for protection against environmental factors.
12. They are more stable at elevated temperature and humidity in contrast to traditional coating techniques.[21]

Demerits

1. In conditions where outer tablet functions as coating over the core tablet (compression coated tablet); the chief demerit of this tableting technology for coating of core tablets, is availability of film coating instead which is simple and more cost effective in prevention of core constituents from environmental factors.[4]
2. Improper centration/off centering of core in outer tablet may be observed; which causes fragile edges.[4]
3. For proper formulation, the weight of the outer tablet must be twice or more in comparison to the weight of core tablet so as to ensure uniform volume and distribution of material surrounding the core. The complication arises if the core contains low density drug substances leading to inappropriate size of formulation which may be difficult to swallow by pediatric/geriatric patients.[4]

IDEAL CHARACTERISTICS OF CORE AND OUTER TABLETS

The weight of outer tablet granules must be twice the weight of core tablet; provisos both have comparable densities and if the core tablet contains low density substances then weight ratio of outer tablet to core tablet can be increased accordingly to provide adequate enclosure of core. The diameter of outer tablet must be 3/32 inches greater than that of core tablet. This will provide 3/64 inches thick covering around the core tablet.[4] The core tablet must be kept as small as possible with any formulation recipe that produce firm tablet allowing any type of granulation technique. The granules for outer tablet must possess meticulous characteristics such as cohesiveness and plasticity, to produce stable formulation physically. They must be sufficiently plastic to expand with the slight expansion of core after ejection of tablet in tablet from die. They must be cohesive enough to adhere over the surface of core tablet. Granule size must be significantly small enough to fill interstices between the core tablet and die wall, for flawless compression. The core must be precisely placed in the center of the outer tablet so as to obtain uniform sturdiness all over.[4]

Core must be in the center of outer tablet. If the tablet in tablet is required to broken along bisect, improper centration will lead to distribution of uneven dose. It will also compromise aesthetic appearance of formulation, if the core is obtruded out of outer tablet due to cocking (tilting) or horizontal/vertical displacement.[20]

RELEASE MECHANISM

The release of drug from the tablet in tablet formulation follows three decisive strides [Figure 6].[22]

(a) During the initial stage of dissolution, the penetration of dissolution fluid causes expansion of outer tablet. (b) In following stage, there is swift penetration of dissolution fluid causes erosion of external surface in outer tablet. Further penetration of dissolution fluid in core tablet, enhances the internal pressure, cause to swell core tablet which leads to rupturing of outer tablet. (c) During final stage of dissolution, there is rapid release of drug from the core tablet.[22]

PROCESSING PROBLEMS ASSOCIATED IN MANUFACTURING OF TABLET IN TABLET

Capping, is one of the most frequently observed processing problem associated with manufacturing of tablet in tablet. This may be because of various reasons. The outer tablet may cap off due to presence of excess amount of fines in granules of outer tablet, during compression. This can be overcome by confining the lubricants, disintegrants to not more than 10% of the batch size recipe as these constituents possess poor cohesive properties.[4] Capping is also experienced, if excessively dried granules are processed. This quandary can be conquered by reducing drying time/temperature or else using binder with good water retention properties (Povidone, sucrose, etc.). Another reason for capping in formulation is, considering high compression force during manufacturing of core tablets. Outer tablet do not bond to the highly densified core moreover high compression force produces elastic core rather than plastic leading to capping on ejection from die due to release of internal stress.[4]

The capping in tablet in tablet formulation could be because of using dilapidated steel dies which had developed compression ring on the interior surface, on the die wall. This compression ring gradually develops on regular usage, at a position where tablet is formed when punches are in compressed position, within the die. In such cases, the diameter of compressed tablet in tablet is slightly higher than the internal diameter of the die, requiring greater ejection force by the lower punch on to the circumference of tablet in tablet, leading to weakening of bond within the tablet in tablet, which results in capping. This situation can be overcome by the use of dies with carbide inserts. The capping in tablet in tablet is also caused by the use of deep concave punches leading to uneven distribution of compression force on the edges and axis of tablet in tablet during high speed compression.[4]

The capping in tablet in tablet may not evident immediately after the compression, it may occur during storage. It can be accessed through friability test carried out past 4 min or forcefully removing, outer tablet from core. The capping in tablet in tablet can also be determined by subjecting tablets through automatic tablet counter twice or thrice.[4]

Improper centration (failure to keep core tablet in the center of outer tablet) is also experienced during manufacturing of tablet in tablet. The core may be off centered (cocking; positioning of core tablet in tilt arrangement, in the outer tablet, off center; horizontally or vertically) due to multiple reasons [Figure 7]. This may be because of poor flow of granules into die cavity, leading to uneven filling. Processing hard granules is also attributed to off center core owing to application of centrifugal

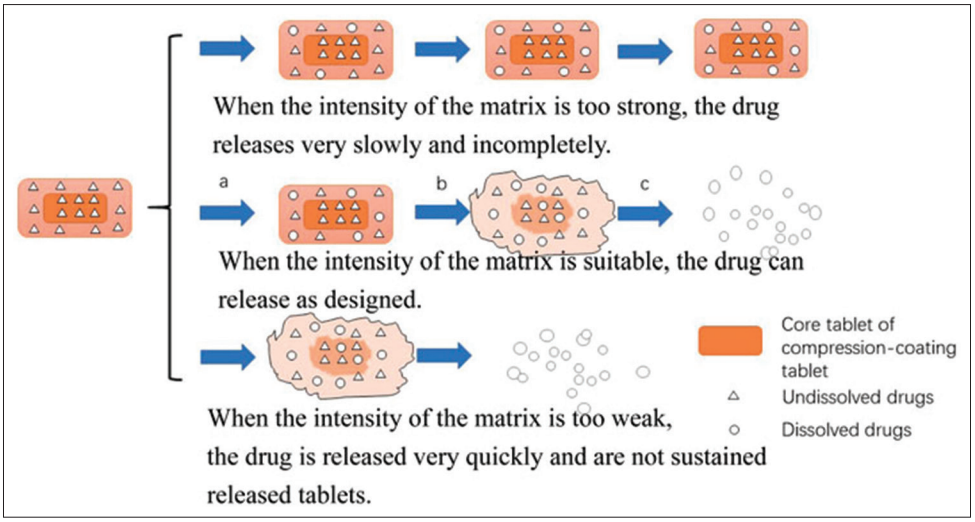

Figure 6: Possible representation of drug release from tablet in tablet[22]

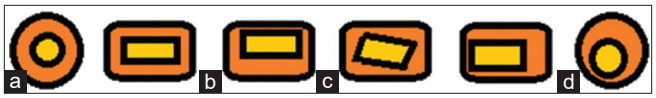

Figure 7: (a) Ideal positioning of core tablet in outer tablet. Improper centration: (b) Unequal positioned c) cocking (d) off centered

force on rotating turrets. Improper centration may be observed if the core composed of waxy substances. Compressing formulation at temperature higher than 75°F softens the waxy core catalyzing sticking in V slots or transfer cups. In such case, core tablets must be refrigerated for 24–48 h before compression or compression must be carried out under low temperature and humidity conditions (RH-35%). Off-centered core in tablet in tablet formulation may also be observer due to mechanics of machine and speed of compression. High compression speed on rotary press produces centrifugal effect on core tablet making it off-centered. It can be overcome by reducing the speed of compression or formulating soft granules of outer tablet with lactose so as to avert sliding of core over lower portion of granules inside the die.[4]

Bound water in formulation constituents may manifest incompatibility issues between core and outer tablet elements. This complication can be overcome using anhydrous excipients and processing tablet in tablet formulation under low relative humidity surroundings. In such cases anhydrous lactose, mannitol must be preferred over sucrose. Prolong or severe drying conditions may be helpful provided constituents are thermostable.[4]

MACHINES TO MANUFACTURE TABLET IN TABLET

The machine to manufacture tablet in tablet formulation uses either previously compressed core tablet or concurrently compress core and then tablet in tablet on the same compression machine. Among machines that uses pre-compressed core tablet are the Colton Model 232 and the Strokes model 538. The Colton Model 232 consists of 33 compression stations to manufacture maximum 900 tablet in tablet/minute with upper diametric limit of 5/8 inches. The Strokes model 538 is 27 stationed, BB2 double rotary, tablet in tablet compression machine, with only one pair of compression rollers. This machine can produce, utmost 700 tablet in tablet/minute with upper diametric limit of 5/8 inches. The Manesty Drycota is D3, 23 stationed presses that simultaneously compresses core on one side of machine which is then conveyed to other side of machine to compress outer tablet over the core. It can produce maximum 900 tablet in tablet/minute with upper diametric limit of 5/8 inches. The main advantage of using the Colton Model 232 and the Strokes model 538; as these machines uses previously compressed core tablets which can be manufactured at high speed compression machine with output as much as 10000 tablets/minute, also these core tablets can be previously qualified for physical and chemical characteristics before subjecting to compression of outer tablet over the core. In this case core must possess significant hardness to withstand bulk transfer but in manufacturing tablet in tablet through the Manesty Drycota, core just firm enough to withstand transfer of core from bridge to outer tablet manufacturing turret. The core tablets produced through Manesty Drycota are porous in nature, hence allowing dissemination of outer tablet particles into core and upon compression produces densified and firm tablet in tablet.[4]

Kilian Prescoter is another tablet compression machine to manufacture tablet in tablet. It has 20 stations and the die table trek at a rate of 15 r.p.m. to produce 300 tablets/minute.[20]

The various API's are used to formulate Tablet-in-Tablet/ Compressed-coating/Press coated technology [Table 1].

EVALUATION OF TABLET IN TABLET

Tablet in tablet formulation is evaluated nearly on same parameters as used for characterizing uncoated tablet, additionally the core tablets must also be evaluated on similar terms before subjecting to final compression of tablet in tablet formulation.

Thickness

The thickness of the core and final tablet in tablet formulation can be measured using sliding micrometer caliper scale. The limit for thickness of both the formulations is ± 5% of standard value.[47]

Weight variation test

The weight variation test is required to be performed on core tablets as well as on final tablet in tablet formulation. For this test 20 tablets are individually weighed and average weight is calculated. They must fall in weight variation tolerance limits given in IP or USP.[47]

Crushing strength

It is the force required to fracture tablet in diametric compression test. The hardness of the core and final tablet in tablet formulation can be assessed using hardness tester, namely, Monsanto hardness tester, Pfizer hardness tester, Strong-Cobb hardness tester, Erweka hardness tester, and Schleuniger hardness tester. The tablet in tablet formulation must possess adequate hardness to withstand abuses during handling and transportation.[47]

Friability

This test is performed by using Roche friabilator which subjected the tablet in tablet formulation to simultaneous

Table 1: Various API's formulated using tablet-in-tablet technology

S. No.	API	Category	Formulation Significance	Year	References
1.	Cyclandelate	Vasodilator	Quickly dispersible drinkable mixture, Protection to API from Environmental factors	1985	[9]
2.	Amoxicillin trihydrate and Clavulanic acid	Antibiotic - β-lactam antibiotic	Chewable tablet, Increase in stability under varied environmental conditions	1998	[23]
3.	Diltiazem hydrochloride	Anti-hypertensive - Calcium channel blocker	Timed-release tablets	2000	[24]
4.	Acetaminophen	Analgesics and Antipyretic	Timed-release tablets	2003	[25]
5.	Nifedipine	Anti-hypertensive - Calcium channel blocker	Time-release formulation	2004	[26]
6.	Fenoterol Hydrobromide	Selective β2 adrenergic receptor agonist- bronchodilator	Extended release formulation	2008	[27]
7.	Nateglinide	Oral Anti hyperglycemic agent	Controlled Release Erosion Matrix Tablet	2009	[28]
8.	Mesalazine	Anti-inflammatory agent	Colon delivery	2010	[29]
9.	Theophylline	Methylxanthines-smooth muscle relaxant, diuretic, bronchodilator, cardiac and central nervous system stimulant	Delayed release dosage form	2010	[30]
10.	Losartan Potassium	Anti-hypertensive - Angiotensin-II antagonist	Time-release formulation	2011	[31]
11.	Diclofenac sodium	Nonsteroidal anti-inflammatory agent	Colon specific delivery	2012	[32]
12.	Carvedilol	Anti-hypertensive - Beta-blocker	Biphasic drug release	2013	[33]
13.	Cefpodoxime Proxetil	Antibiotic - Cephalosporin	Gastro retentive formulation	2013	[34]
14.	Flurbiprofen	Nonsteroidal anti-inflammatory agent	Colon specific delivery	2013	[35]
15.	Glipizide	Antidiabetics - sulfonylurea	Controlled release formulation	2013	[36]
16.	Captopril and Hydro chlorothiazide	Anti-hypertensive - Angiotensin converting enzyme inhibitor. Thiazide diuretic.	Rapid release HCTZ and slow sustain release of Captopril	2014	[37]
17.	Ketorolac tromethamine	Nonsteroidal anti-inflammatory agent	Colon specific delivery	2014	[38]
18.	Pioglitazone hydrochloride	Antidiabetics-Thiazolidenediones	Pulsatile drug delivery	2014	[39]
19.	Salbutamol sulphate	Selective beta2-adrenergic receptor agonist - Bronchodilator	Pulsatile drug delivery	2014	[40]
20.	Orlistat and Venlafaxine hydrochloride	Gastrointestinal lipase inhibitor antidepressant	Chewable tablet-in-tablet	2015	[41]
21.	Ofloxacin	Antibiotic-fluoroquinolone	Controlled release Floating tablets	2015	[42]
22.	Prednisolone	Corticosteroid	Colon Targeting	2016	[43]
23.	Lansoprazole and Acetylsalicylic acid	PPI NSAID	Overcome Side effects (Ulcer) of acetylsalicylic acid	2016	[44]
24.	Mesalamine and Prednisolone	Topical anti-inflammatory agent Synthetic glucocorticoid	Colon specific delivery	2017	[45]
25.	Paliperidone	Atypical antipsychotic	Controlled ascending release	2018	[46]

attrition and impact during rotation in plastic chamber for 100 revolutions. Weight loss <0.5–1% is acceptable.[47] Carrying out this test, past 4 min is also helpful in predicting capping within tablet in tablet dosage form.[4]

Radial tensile strength

Radial tensile strength of tablet in tablet can be determined by hardness tester. The formulation is required to be kept

under dehumidified conditions in desiccator for 24 h with suitable desiccant.[48] The diametric compression test is performed to predict maximum fracturing load P. This value is further used to predict radial tensile strength σ_0 using following equation:[49]

$$\sigma_0 = \frac{2P}{\delta Dt}$$

D = Diameter of the tablet in tablet.
t = Thickness of the tablet in tablet.

Internal intensity

Internal intensity of tablet in tablet can be predicted using constant load boring intensity tester. The drill with tip diameter 1mm is intruded in to the tablet in tablet with 150 g of load at 200 rpm. The relative internal intensity can be determined through drilling speed.[48]

Drug content uniformity test

This test is performed to ensure consistent potency in low dose tablet in tablet formulations. According to this test 30 tablets of tablet in tablet formulation are erratically picked from batch. 10 of them are individually analyzed for drug contents, according to official compendia. 9 tablets out of 10 must with in ± 15% of labeled value. Tenth tablet may fall in ± 25% of labeled value. If this criteria are not realized then remaining 20 tablets of tablet in tablet should analyzed individually for uniformity in drug contents. None of the tablet should fall out of ± 15% of labeled value.[47]

Disintegration test

This test is design to steer and plan the finest recipe of the tablet in tablet formulation. It is also an in process control analysis to reassure batch to batch consistency. The test is executed on USP 6 tube disintegration test apparatus. For the acquiescence of this test, the tablet in tablet formulation necessarily disintegrates and all subdivisions must pass through screen within a specified time.[47]

Dissolution test

This test is executed to study in vitro drug release and rate of drug release from the tablet in tablet formulation in simulated gastric or intestinal environment.[47] The test is performed on USP apparatus I or II at 50–100 rpm. The sample is required to be drawn at different time intervals and simultaneously same amount of fresh dissolution fluid is added to maintain sink conditions. The samples are subjected to filtration through 0.45 µm Millipore filter before analyzing spectrophotometrically or as per official compendia.[22]

Erosion and absorption studies

This test is performed on USP type-I dissolution test apparatus. The tablet in tablet formulation is assessed through gravimetric analysis. The testing conditions and dissolution media will remain same as considered in dissolution testing. The sampling time points are decided. The six tablets of the tablet in tablet formulation are introduced in USP type-I apparatus. The tablet in tablet formulation is withdrawn at particular sampling time point and dried at 60°C till invariable weight is attained. Fresh tablets of tablet in tablet formulation are required to be introduced in dissolution test apparatus at subsequent sampling pull points.[22]

The erosion can be calculated using % remaining mass (RM) using the following equation: [22]

$$\%\ RM = \frac{Wr}{W0} \times 100$$

And the swelling ratio (SR) is employed to elucidate the water uptake by tablet in tablet formulation and its expansion process. The swelling ratio can be calculated through following equation: [22]

$$\%SR = \frac{Wt - Wr}{Wr} \times 100$$

W_0 = initial weight of fresh tablet in tablet formulation.
W_r = weight of remaining dried tablet in tablet formulation after entering the media at time t.
W_t = weight of tablet in tablet formulation without water on the surface at time t.

CONCLUSION

Tablets are the most extensively used formulation amidst all dosage forms because of its precise dosing, convenience to use, and low cost. The tablet in tablet technique is an innovative and pragmatic approach, where a tablet is compressed with a core tablet in the center. This technique is recognized by different names or terms, namely, OSDrC, press coated tablet, compression coated tablet, single/bilayer core containing tablets, compression embedding technique, and dry coating. This technique may serves as coating over the core tablet but offer multiple advantages over conventional pan coating technique. The key benefit of this technology is, exclusion of water/solvent during coating, thus there is no core softening or undesirable chemical reaction because of water/solvent penetration into the core tablet. The core tablet is coated by compression in single step thus eliminating various time consuming steps (diverse alternative steps of coating and drying) followed during conventional pan coating. There are many formulations developed as well as approved patents using tablet in tablet technology but

still it can be explored in developing formulations in which both API's (in core and in outer tablet) work in synergy and produce meaningful pharmacological outcome besides improving patient compliance.

AUTHORS DISCLOSURE STATEMENT

The authors have no conflict of interest to disclose.

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Source of Support: Nil. **Conflicts of Interest:** None declared.