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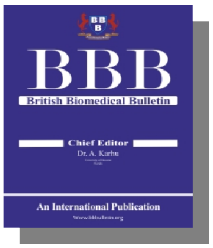

Review

Novel Approach in Compressed-coated Tablet Dosage Form: Core-in-Cup (In Lay) Tablet with Geometrically Altered Drug Delivery Concept

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A B S T R A C T

In past few years, chemical entity often is first formulated as a free-flowing granulation for encapsulation within hard gelatin capsules. Very conventional ideas has been used for the deployment of the drug likewise single dosage form with API and excipient, one dosage form for only one disease etc. so duration of course and treatment of the disease maximized.so for the minimization of that there are number of innovations and new approach has been profound.Tablets are the most preferred and widely used dosage form because of their ease of administration, lower cost of manufacture, and elegance. So in this article, we describe the general characteristics, introduction and evaluation of in lay tablet which is one type of modification in compression-coating. The compression-coating granulation or blend can be preformulated to provide desired functionalities to the coating. The only requirement for producing the compression-coated tablet dosage form described herein is that the core material should possess the ability to flow into a die during production.

Introduction

Modified or controlled release oral drug delivery systems have, over the last few decades, been shown to offer advantages over conventional systems. These include increased patient compliance, selective pharmacological action; reduced side-effect profile and reduced dosing frequency. These systems may therefore have a significantly beneficial outcome in therapeutic efficacy. Controlled release offers prolonged delivery of drugs and maintenance of plasma levels within a therapeutic range Furthermore, by pairing drug administration rate with drug elimination rate, steady-state plasma levels can be maintained[1,2].

Currently most drug delivery systems exhibit first-order drug release kinetics where the plasma level of the drug is extremely high after administration and then decreases exponentially. This poses disadvantages such as minimal therapeutic efficacy due to reduced drug levels; or drug toxicity which can occur at high concentrations[3]. This type of drug release does not allow for appropriate plasma drug level balance. Peak-to-trough fluctuations (as described in Figure 1) may occur with first-order drug release that may cause dose dependent side effects.Drug delivery systems should ideally exhibit zero-order drug release kinetics which allows for a constant quantity of drug to be released over an extended period of time, resulting in uniform and sustained drug delivery. Zero-order is a desired drug release kinetic in antibiotic delivery, the treatment of hypertension, pain management, antidepressant delivery and numerous other conditions that require constant plasma drug levels. Thus, various studies have been undertaken attempting to develop systems that are easily able to provide zero-order or near zero-order drug release[5,6].

The utilization of geometric principles have for many years been considered and employed in order to modify drug release behaviour from non-linear to zero-order or near zero-order release kinetics. Thus far researchers have attempted to control dissolution behaviour of drug delivery systems by modifying and controlling the geometry of the employed devices e.g., geometries such as spherical, cylindrical, holed cylindrical and biconvex devices[7].

TABLET AS A DOSAGE FORM

Tablet is a solid dosage forms each containing a unit dose of one or more medicaments with or without suitable excipients.

Tablets may be swallowed whole or being chewed. Some are dissolved or dispersed in water before administration. Some are put in oral cavity, where the active ingredient is liberated at a predetermined rate. Implants or passeries may also be presented in form of tablet.

Tablet may vary in shape and differ greatly in size and weight depending on the amount of medicinal substance and the intended mode of administration[3].

Advantages

- Accuracy of dose is maintained since tablet is a solid unit dosage form tailor made release profile can be achieved.
- Longer expiry period and minimum microbial spillage owing to lower moisture content.
- As tablet is not a sterile dosage form, stringent environmental conditions are not required in the tablet department.
- Organoleptic properties (taste, appearance and odour) are best improved by coating of tablet.
- Large scale manufacturing is feasible in comparison to other dosage forms. Therefore, economy can be achieved.

- Product identification is easy and markings done with the help of grooved punches and printing with edible ink.
- Different types of tablets are available like buccal, floating, colon targeting, effervescent, dispersible, soluble, and chewable, etc.
- Ease of packaging (blister or strip) and easy handling over liquid dosage form.
- Easy to transport in bulk. Emergency supply supplies can be carried by patients.
- In composition to parenteral dosage form, a doctor or a nurse is not required for administration. I e. self-administration is possible.

Disadvantages

- Difficult to formulate a drug with poor wettability, slow dissolution into a tablet.
- Slow onset of action as compared to parenterals, liquid orals and capsules.
- The amount of liquid drug (e.g. Vitamin E, Simethicone) that can be trapped into a tablet is very less.
- Difficult to swallow for kids, terminally ill and geriatric patients.

Benefits of Modified Release Tablets

The novel system of drug delivery offer a meansof improving the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and / or targeting the drug to desired site.

- Decreased in dosing frequency
- Reduced peak to trough ratio of drug in systemic circulation.
- Reduced rate of rise of drug concentration in blood.
- Sustained & Consistent blood level with in the therapeutic window.
- Enhanced bioavailability
- Customized delivery profiles

  Reduced side effects

Multilayered Tablets for Controlled Drug Delivery

Mutilayered systems (bilayered, triple-layered, quadruple-layered, etc.) are becoming increasingly recognized as controlled-release drug delivery systems. Namdeo expressed that multilayered tablets have demonstrated promise, possessing various benefits, namely the ability to prevent interactions between drugs and excipients; and by providing an array of release profiles in one delivery system of either the same or different drugs, treatment for conditions that require a regimen of more than one drug, immediate drug release using a disintegrating monolithic matrix in order to achieve an initial peak in plasma drug level, delayed drug release using an eroding monolithic matrix which may deliver another active drug to a different part of the gastrointestinal tract, providing controlled drug release instituting as well able monolithic matrix and better control and regulation of release profiles by retarding initial burst release and achieving zero-order kinetics[17]. It would be beneficial if research focused on further modification of these systems for improved and comprehensive drug release capabilities that enable a larger scope ofapplication in drug delivery.

Controlled-release multilayered tablets typically involve a drug core layer that is surrounded by barrier layers that may be made up of hydrophilic swellable polymers such as Hydroxypropyl-methyl cellulose (HPMC) and poly(ethylene oxide) (PEO) or hydrophobic polymers such as ethyl-cellulose (EC)[8]. The barrier layers minimize and therefore delay the interaction of the gastrointestinal environment with the active core, by decreasing the surface area available for drug release or by controlling the rate at which the solvent penetrates the layers[9,10]. This allows the initial burst release to be minimized and therefore the drug release can be controlled at a near constant

level while the barrier layers undergo erosion or swelling[9]. The swollen barrier layers undergo erosion as time goes on, thus increasing the surface area which ultimately allows more drug to be released. Following the same principle, it is possible to obtain a constant release profile as well as other types of dissolution patterns such as pulsatile or delayed delivery as well as extended drug delivery depending on the characteristics of the polymers employed. In either case the system should ideally erode completely (i.e., leaving no residue in the gastrointestinal tract after the entire amount of drug is released).

TOOLING

To demonstrate proof-of-concept of the compression-coated tablet process, 9/16-in. tooling from a single punch press was modified (see Figures 1 and 2) to simulate the special hollow tooling with the core rod shown in Figure 3. Three punches were machined, as shown in Figure 1a, to simulate the shape of the punch tip presented to the powder bed in the die when the core rod is in the ex- tended position shown in Figure 3a. These three punches were machined to various dimensions to produce cups with a thick wall (4.8 mm), intermediate wall (4.1 mm), or a thin wall (3.2 mm). Another punch was machined as shown in Figure1b to mimic the shape of the punch tip in the retracted position of the tooling with the core rod as shown in front and side views in Figure 3b. Figure 2 shows the specially machined punches. The lower punch was an unmodified flat-faced punch (not shown)[3,4].

INLAY TABLETS

A type of layered tablet in which instead the core tablet being completely surrounded by coating, top surface is completely exposed. Tablet compressing was done with core rod tooling in which only one surface of core is expose to outside and other drug is incorporated in cup portion. While preparation, only the bottom of the die cavity is filled with coating material and core is placed upon it[11,12]. The main body portion may consist of an uncoated granulation which is compressed around the enteric coated inlay portion In this modification the main body portion of the tablet is first released and assimilated in the gastrointestinal tract while the enteric coating protects the inlay portion for a predetermined period of time so as to provide time delayed or sustained medication. Atoz is offering Inlay tablets with combinations like Metformin 500mg sustained release (Outer coat) and Pioglitazone 15 mg (core tablet) which has a very unique advantage.

Advantages of inlay tablets

- Dosage form comprising of an active ingredient as modified release and an active ingredient as immediate release can be prepared.
- Has the ability to release soluble and insoluble drugs at a zero-order rate of release in dissolution media .Dosage frequency of highly water soluble drugs con be reduced providing same efficacy.
- Tablets of different shape such as triangular, rectangular, or capsule shaped tablets can be manufactured.
- Adverse effects due to sub therapeutic plasma concentration can be avoided.
- Plasma level can be maintained constant and within the therapeutic window throughout the period of treatment.
- The burst effect, namely, large release within a short period of time, is common in highly soluble drugs, and shall be avoided, as it may lead to high concentration of active ingredients in the blood stream.

PREPARATION OF THE COMPRESSION-COATED TABLETS

A carefully weighed amount of powder blend (hereinafter referred to as the coating blend) was placed in the die and compressed on a Carver Press (Wabash, IN) at a known force with the tooling shown in Figure 3a to produce a cup-shaped tablet (cup). The cup was left within the die, and a known amount of either a model drug or a blend containing the drug was placed inside the cup and tamped lightly with the punch in an ex- tended position. A weighed amount of the coating blend was placed on top of the die contents, and the cup was compressed for a second time with the punch in a retracted position at a known force to produce the final compression-coated tablets (see Figure 3b).

1. Triple-Layered Tablets

Triple-layered tablets are comprised of an inner drug core layer which is sandwiched between two surrounding barrier layers[13]. These barrier layers may also contain drug and serve as matrices to release drug in various release patterns[6,7]. The general mechanisms of action of triple-layered tablets include erosion of matrix layers, creation of a drug concentration gradient, limiting surface area of release of the swellable matrix by the barrier layers, erosion and swelling of the barrier layers to achieve a constant area for uniform drug release, as well as varying of the layers dissolution to achieve pulsatile or alternating release profiles[14,16]. Triple-layered systems have some rewards in contrast to typical systems due to the varying release pattern capability, simplicity of manufacturing, reduced dosing frequency that leads to enhanced patient compliance, enhanced safety profile of drug levels and reduced cost.

2. Core-in-Cup Devices

Danckwerts developed a core-in-cup tablet system that was able to provide zero-order drug release of aqueous-soluble and aqueous-insoluble drugs. The system consisted of a disc-shaped matrix core that was compression-coated on one surface as well as at the circumference in order to form a cup around the core. Drug was released in a sustained manner from one stable surface that had a constant surface area. By manipulating the grade, quantity and exposed surface area of any hydrophilic polymer or mixture of polymers that erode constantly over time, the core-in-cup compressed tablet is able to deliver a constant amount of drug over time[17]. Results showed that the system was able to provide zero-order drug release for time intervals between 8 and 23 hours, the time of linear release was approximately 8 hours when 5% w/w HPMC K4M with caffeine core-in-cup tablets were produced and approximately 23 hours when 15% w/w HPMC K15M in ibuprofen core-in-cup tablets were produced. The research that has been conducted on core-in-cup devices showed several interesting and useful techniques as well as beneficial application in terms of the solubility of drugs, the flexibility of delivering both aqueous soluble and aqueous insoluble drugs pose an advantage. Danckwerts also studied the effectiveness of cup tablets of different depths for use in core-in-cup tablets and the optimal formulation in terms of drug release behaviour. He developed a specific punch that is able to change the depth of the cup tablet, thus allowing it to carry various cores in terms of hardness and mass. The efficiency of cup tablets with varying depths and the optimal formulation in terms of drug release were investigated in the study.[18,20] The cup tablets were composed of 15% w/w carnauba wax in EC while the core tablets were composed of 5% w/w HPMC K4M in ibuprofen. The results indicated that Ibuprofen was released at a near zero-order rate for 18 hours for the cup tablets that had a final depth of 4mm[19,26].

Figure 6 shows the typical geometries of core-in-cup tablets.

3. Divided Core Tablets

There also possible to make divided tablets with separate cores in one step operation, which is not possible with current technology. For example divided enteric coated tablets are the world's first dividable enteric coated tablets. Dividable core tablets so called because the core fully encased in the coating even when the tablet is divide, even though the release profile is remain unaffected by dividing the table[22].

4. Cored Tablets with Poorly Compressible Cores

By using this technology there is no need of separate manufacturing of core tablet even using of powders with poor compressibility as the core matrix. As it possible to directly encase core pharmaceutical ingredients with the outer covering, these ingredients can be used in oral rapid disintegration tablets.

Pellets can also be used instead of powder as core material, drugs normally formulated as capsule dosage form can be formulated as tablet dosage form[22].

5. Procise® Technology (Geometrically altered drug delivery system)

The Procise® device has a specific geometric configuration (as depicted in Figure 7) that controls drug release behaviour[19]. It is composed of a core which contains uniformly dispersed drug with a core hole in the middle (Figure 7). It has been made known that, altering the geometry of the core can change the drug release kinetics into zero-order or even first order if desired the core's entire surface besides the surface of the cylindrical face is surrounded by a permeable inactive coat so that drug release occurs solely from the cylindrical area. The device is also able to deliver up to two drugs simultaneously with varying release profiles.24 This technology further adds to the varied geometrical systems for flexible and simplified drug delivery.

EVALUATION OF INLAY TABLETS

The following standards or quality control tests should be carried out on compressed tablets:

- General appearance
- Content uniformity
- Mechanical strength of tablets
- Disintegration
- Dissolution
- Swelling and erosion test

Others are content uniformity, friability, weight variation, organoleptic properties etc.

1. Disintegration Test

The U.S.P. device to test disintegration uses 6glass tubes that are 3" long; open at the top and 10 mesh screen at the bottom end. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 20°C such that the tablet remain 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. Move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet. According to the test the tablet must disintegrate and all particles must pass through the 10 mesh screen in the time specified. If any residue remains, it must have a soft mass. Disintegration time: Uncoated tablet: 5-30 minutes Coated tablet: 1-2 hours[23].

2. Dissolution Tests

A) Apparatus-1 (Basket Type)

A single tablet is placed in a small wire mesh basket attached to the bottom of the shaft connected to a variable speed motor. The basket is immersed in a dissolution medium (as specified in monograph) contained in a 1000 ml flask. The flask is cylindrical with a hemispherical bottom. The flask is maintained at 37±0.5^{0}C by a constant temperature bath. The motor is adjusted to turn at the specified speed and sample of the fluid are withdrawn at intervals to determine the amount of drug in solutions[25].

B) Apparatus-2 (Paddle Type)

It is same as apparatus-1, except the basket is replaced by a paddle. The dosage form is allowed to sink to the bottom of the flask before stirring. For dissolution test U.S.P. specifies the dissolution test medium and volume, type of apparatus to be used, rpm of the shaft, and time limit of the test and assay procedure for. The test tolerance is expressed as a % of the labelled amount of drug dissolved in the time limit[25].

3. Swelling and Erosion Tests

Measurement of swelling and erosion rates of inlay tablets was carried out, after immersion of tablets in the test medium.

Weighed Tablets (W0) were placed in the closed plastic containers with the mesh underneath the tablets, rotating at specified rpm with the specified conditions of dissolution medium and time.

Each container was removed from the incubator, the tablet with the mesh was withdrawn from the medium and blotted to remove excess water and then weighed (W1) on an analytical balance.

The wet samples were then dried in an oven at specified temperature for certain time, allowed cooling in a desiccators and finally weighed until constant weight was achieved (final dry weight, W2).

The experiment was performed in triplicate for each time point and fresh samples were used for each individual time point. The percentage increase in weight due to absorbed liquid or water uptake was estimated at each time point from following equation:

$$\%\text{weight change} = W_1 - W_0 \text{ X } 100 / W_0$$

The percentage remaining of tablets after erosion (ES) was calculated from following equation:

$$\% \text{ Remaining} = 100 - ES$$

4. Measurement of radial swelling

An inlay tablet was placed in identical conditions as described under axial swelling, but with a standard scale (in mm) placed underneath the petri dish. Visual measurements of the diameter were taken at 30 min time intervals for 360 min over the swelling period[22].

5. Morphological examination of swollen tablets

Morphological examination of the swollen tablets was carried out using a digital camera equipped with zoom lens EF-S 18–55 mm. Photo imaging was performed on eachtablet formulation after hydrating in 0.1 N HCl or pH 6.8 phosphate buffer for 30 min. The tablets were taken out from the medium and were imaged by a digital camera. Under the same optical conditions, an image of a linear scale was used to calibrate[22].

6. Measurement of axial swelling

A single inlay tablet was placed on a glass slide in a petri dish (60 mm in diameter) containing 30 ml ofmedium specified maintained at given temperature in a thermostatic water bath. The lateral edge of

the inlay tablet was photographed at 30 min time intervals for 360 min. The swelling distances were measured directly from the photographs using the thickness of the glass slide as are ference.[22]

PATENTED INLAY TABLET FORMULATIONS[26]

1. Pravastatin Sodium (10mg) + Niacin (500mg)
2. Pravastatin Sodium (10mg) + Niacin (1000mg)
3. Lamotrigine (25mg) + Sodium Valproate (500 mg)
4. Lamotrigine (25mg) + Sodium Valproate (1000 mg)
5. Rosiglitazone Maleate (2mg) + Metformin Hydrochloride (500mg)
6. Rosiglitazone Maleate (2mg) + Metformin Hydrochloride (1000mg)
7. Rosiglitazone Maleate (4mg) + MetforminHydrochloride (500mg)
8. Rosiglitazone Maleate (4mg) + MetforminHydrochloride (1000mg)
9. Glimipride (1mg) + Metformin Hydrochloride (500mg)
10. Glimipride (2mg) + Metformin Hydrochloride (500mg)

APPLICATIONS OF INLAY (CORE IN CUP TABLETS)

1. Novel Controlled Release Formulation for Highly Water Soluble Drug Tramadol HCl

Tramadol, a synthetic opioid, is a dual action analgesic agent. Despite a good oral bioavailability (75%) and moderate elimination half-life (5.5hrs.), Tramadol needs frequent oral dosing throughout the day (50 mg/4-6 hrs.).

High aqueous solubility causes the rapid diffusion of drug from sustained release formulations.

A novel and robust controlled release formulation of Tramadol HCl to reduce the dosing frequencycan be prepared.

Developed formulation of Tramadol HCl showed controlled release in-vitro behaviour with a release profile of less than 15% for initial two hours (retarding initial burst) followed by a controlled complete release in controlled manner.

Developed formulation could be novel alternative to traditional immediate release formulations of tramadol is stable, convenient to manufacture and cost effective forcommercial use.

2. A hypnotic tablet with Pentobarbital and Mephenesin

The outer layer with uncoated granulations ispromptly disintegrable for immediate hypnotic effect and the inlay portion with an enteric coating or envelope around begins to disintegrate after three to four hours to maintain or continue the desired effect.

3. An appetite depressant tablet with Amphetamine sulphate and Amobarbital

In the outer layer the particles of the granulationare enteric coated to provide slow release over a period often to twelve hours. The inlay portion is formed from an uncoated readily disintegratable granulation for immediate therapeutic effectiveness.

4. Inlay Tablets Containing Sumatriptan Succinate and Naproxen Sodium.

5. Rosiglitazone IR + Metformin SR Tablet.

6. An oral decongestant tablet containing Phenylpropanolamine hydrochloride Pyrilamine maleate and Pheniramine maleate[25,27].

Conclusion

The compression-coated tablet process provides a means of compression coating by simple modifications to a three-layer press. There are many advantages of this process over traditional compression coating. Separate formation of a core is not required, and therefore no transfer mechanism is required for the core. Similarly, cantering of the core is not a problem in this process, thereby leading to better reproducibility of re-lease profiles in controlled-release applications.Inlay tablet is the dosage form comprising of anactive ingredient as modified release and an active ingredient as immediate release with the ability to release soluble and insoluble drugs at a zero-order rate of release in dissolution media. Dosage frequency of highly watersoluble drugs can be reduced providing same efficacy. Thus any combinations drug combinations can be used with no interactions. Main problems of formulation of drugs like frequent dosing, interactions, burst effect can be reduced. The fact that drug delivery systems with altered geometric configurations (particularly tablets) have shown promising results in drug delivery technology and ease of manufacturing is an added advantage to the pharmaceutical industry.

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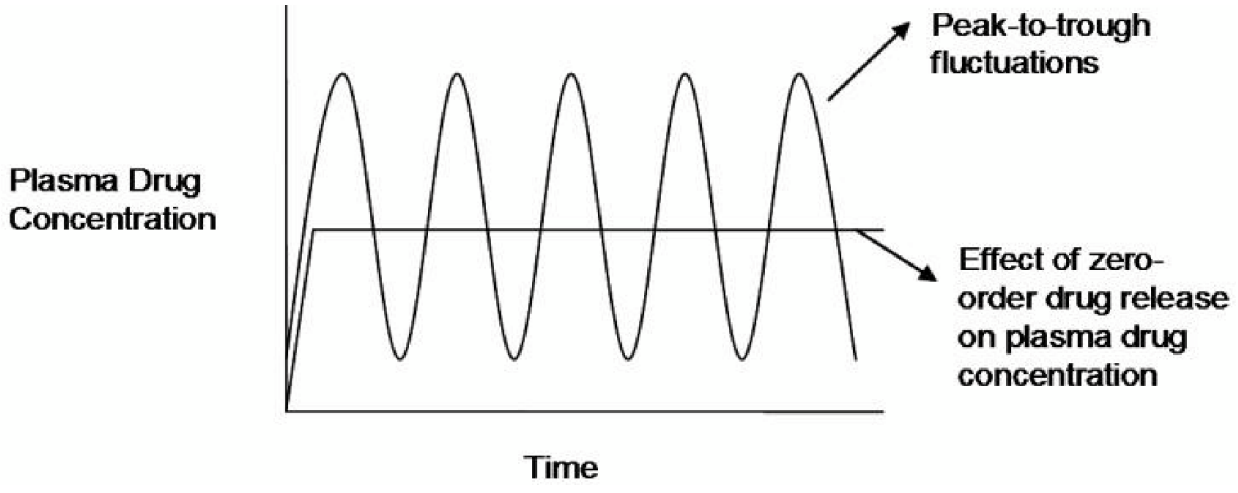

Figure 1. Plasma drug concentration versus time profile exhibiting the effect of zero-order drug release on plasma drug levels (adapted from Shahiwala *et al*.[15])

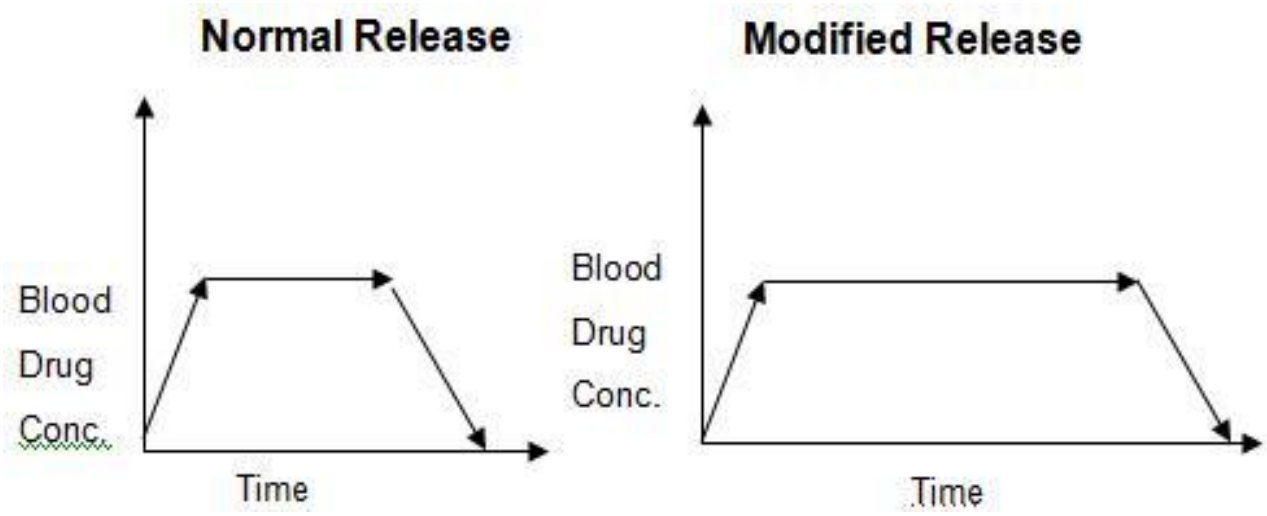

Figure 2. Comparison of concentration of drug with different release study

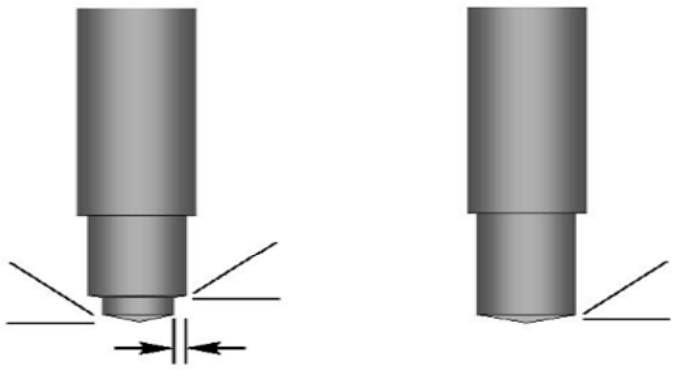

Figure 3. Upper punches for producing prototype compression-coated tablets on a Carver press: (a) construction of the punch used to make a cup and (b) construction of apunch used for the final compression

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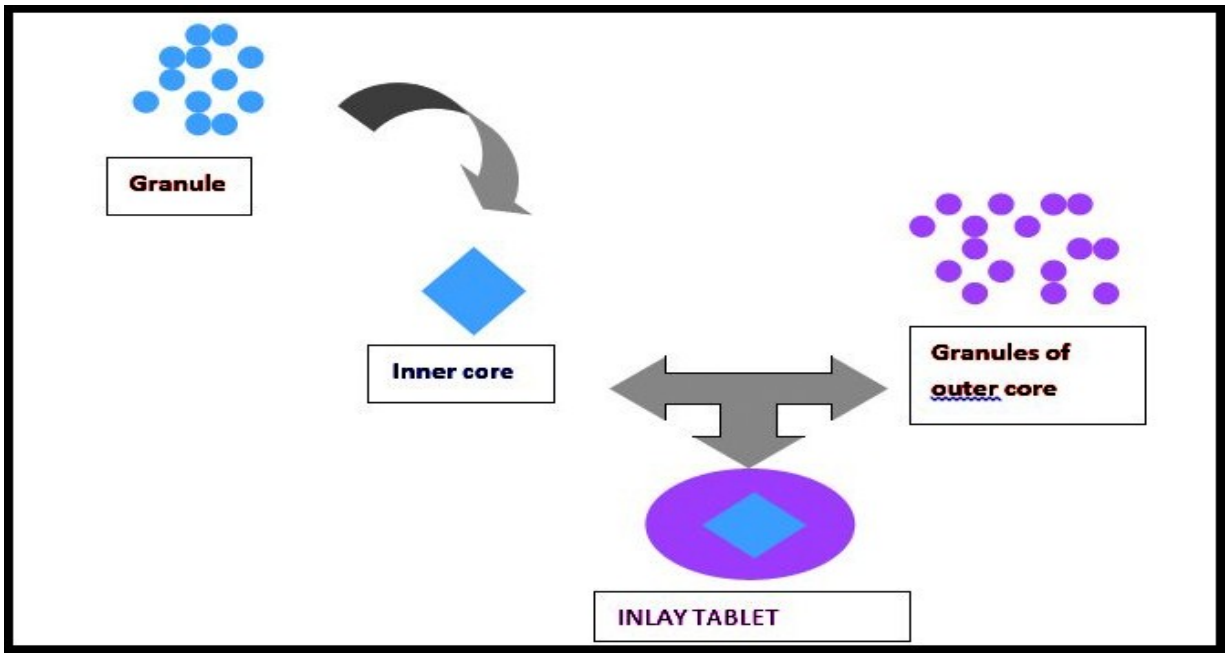

Figure 4. Photo of the tooling used to demonstrate proof-of-concept, a cup, and afinished dosage form

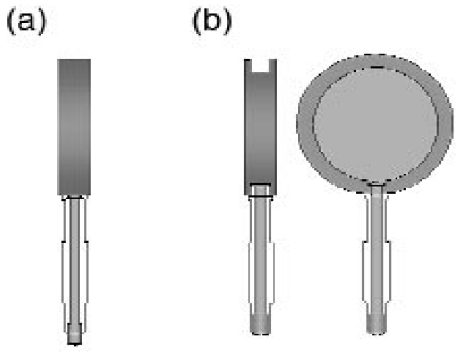

Figure 5. Schematic of a hollow upper punch with a core rod showing (a) the side view of a punch tip in the extended position and a traditional solid roller and (b) the side and front views of a punch tip in the retracted position and a recessed roller.[1-4]