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**Nabeel Shahid**
Faculty of Pharmacy, the University of Lahore
Lahore, Pakistan

**Sajid Ali**
Faculty of Pharmacy, the University of Lahore
Lahore, Pakistan

**Maryam Shabbir**
Faculty of Pharmacy, the University of Lahore
Lahore, Pakistan

**Kiran Waqar**
Faculty of Pharmacy, the University of Lahore
Lahore, Pakistan

**Correspondence:**
**Maryam Shabbir**
Faculty of Pharmacy, the University of Lahore
Lahore, Pakistan

# Compressed coated polypill with mucoadhesive core for cardiovascular disease – A review

**Nabeel Shahid, Sajid Ali, Maryam Shabbir, Kiran Waqar**

**Abstract**
A recent concept of polypill has evolved to include a number of key drugs in a single pill that can be used to prevent various diseases, especially cardiovascular diseases. Modeled economic analyses propose that such multidrug regimen would be cost effective in reducing the cardiovascular diseases in developing countries like India and Pakistan. Recently it has been recognized by Combination Pharmacotherapy and Public Health Research Working Group, the WHO and the World Heart Federation to use polypill on high-risk patient, with or without previous cardiovascular events. Various techniques have been proposed and developed to improve the coating and mucoadhesion techniques of polypill for greater adherence and bioavailability of drug at the site of action. The Compression Coating or Press Coating technique are undertaken to formulate polypill ensuring safety and efficacy. The present article signifies the importance of polypill in cardiovascular diseases and the coating techniques for the development of polypill.

**Keywords:** Polypill, fixed dose combination, cardiovascular disease, press coating, mucoadhesion

## 1. Introduction
Polypill is a fixed dose combination (FDC) which contains three or more medications in a single pill with the purpose of minimizing the numbers of dosage forms tablets or capsules to be taken by the patient. Polypill is a fixed dose combination (FDC) which contains three or more medications in a single pill with the purpose of minimizing the numbers of dosage forms tablets or capsules to be taken by the patient. A polypill concept for minimizing the cardiovascular disease (CVD) risks was first proposed by Wald and Law [1] and has been applied to pharmaceutical preparations [2].

The notion of fixed dose combination pill or the polypill for the preclusion of cardiovascular disease was first anticipated by Wald and Law [1], they by utilizing data and publications draw their own meta-analysis and claimed that a polypill consisting of six components administered to each individual with cardiovascular disease (CVD) over the age of 55 could reduce the occurrence of cardiovascular disease (CVD) by more than 80%. Subsequently, an outburst of controversy has surrounded this idea. A polypill containing three generic components could be an attractive option for the doctors and patients already taking these medicines separately [3].

Lipid lowering agents, antihypertensives and antiplatelets medications have proved to be effective in reducing the cardiovascular diseases. In 2002 Yusuf anticipated that the use of four drugs consisting of a statin, Aspirin, a beta blocker and an ACE inhibitor could result in 75% reduction in cumulative patient risks of CVD events [4]. Wald and Law [1] in an extensive publication anticipated the combination of six drugs "Polypill" that could reduce the risks of ischemic heart disease (IHD) events by 88% and stroke by 80%. The polypill they proposed consists of three antihypertensive agents, Aspirin, a statin and a folic acid [4].

The prevention of cardiovascular diseases with the drug therapy including lipid and blood pressure lowering and antiplatelet therapy is well known. Wald and law [1] have proposed these three treatments in combination with folic acid in a "Polypill". The underline reason is to check the efficacy of these drugs when combined together have synergistic effects. This concept of polypill has created an interest worldwide with critics that this concept would be too optimistic [5].

Among all the non-communicable diseases cardiovascular disease (CVD) is the most common cause of death in low and middle income countries including Iran. Cardiovascular disease (CVD) management is expensive and cost of which is increasing day by day with the advent of new drug therapies. This increases the urgency for possible cardiovascular diseases (CVDs) preventing strategies to reduce morbidity and mortality in low and middle income countries. The concept of "Polypill" among all proposed strategies is being much uncertain since it was proposed by Wald and Law (2003). A meta-analysis has clearly shown that the concept of

polypill formulation can reduce the mortality due to ischemic heart disease (IHD) and strokes by 30-53% [6].
Cardiac events including heart attacks and strokes nearly affect half of the population in Britain. Randomized trials have shown that three classes of drugs including antilipidemics, antihypertensive and antiplatelets have greatly minimized the potential risks of IHD event and strokes. Here we describe the strategy for the prevention CVD based on principles: a daily treatment, the Polypill, containing six components. The polypill would be suitable for peoples with CVD and for every one over the age of 55 [1].

### 1.1 Why need polypill?

The use of statin, an antiplatelet and blood pressure lowering drugs reduce the ischemic heart disease (IHD) morbidity and mortality is with strong evidential support. The efficacy of this treatment is reduced by the poor adherence to the proposed medications, treatment cost and inadequate drug prescribing. In many patients the number of medications seemed to be irresistible. Complex regimen and multiple medications are the major factors for poor compliance. Pill burden or number of medication reduction has proven to be advantageous in improving medication adherence. Fixed dose combinations and simplification of treatment therapies in reducing the pill burden and frequency of dosing intervals is well established. Fixed dose combination medications are the combination of two drugs in a single tablet for reducing the pill burden and complexity of regimen have shown improved adherence by 19% in people with high blood pressure after 12 months. Currently two different type of polypill formulations with four different drugs combined are being trialled in New Zeeland [7].

## 2. Advantages of polypill [8, 9]

The polypill may have several advantages as follow:

### 2.1 Improved delivery of care

This is achieved evading complex procedures to identify patients for therapy, increasing the ease of prescribing and avoiding multiple steps of dosage adjustment for each dose. While such advantages are yet to be proven a study conducted in ischemic heart disease (IHD) or diabetes mellitus patients in USA showed that a simplified therapy includes fixed dose of statin and ACE inhibitor delivered by minimal physician visits, lab tests, dosage titration reduced the risks of ischemic heart disease (IHD) and stroke within 1 year.

### 2.2 Improved adherence

As the number of pills is reduced to just only one per day for cardiovascular disease (CVD) patient the adherence to therapy is much more positive. However it is not proven and increasing the adherence is much more complex and require further study.

### 2.3 Reduced Cost

The polypill is supposed to be less costly using generic components (estimated at ≈ $1 a day in developed and > 20 cents in developing countries) likely to be much lesser then the cost of individual drugs. Reduced cost is authenticated by reduced packaging needs, distribution needs and marketing costs with fewer visits to the prescribers and laboratory tests.

### 2.4 Use of polypill as a platform for novel approaches to widespread cardiovascular disease (CVD) prevention

Today global epidemics cannot be scaled to tackle by current cardiovascular disease (CVD) preventive measures and therapy. Novel approach that utilizes trained non physician health workers to deliver polypill with a handful of lifestyle advises in moderate risk individuals and in cardiovascular disease (CVD) patients. Such focus will reach a much broader and a large impact on at risk patients.

## 3. Pharmaceutical coating techniques for polypill formulation

Pharmaceutical coatings are critical tools to achieve the desired formulation of pharmaceutical dosage forms. Greater aesthetic property of a dosage form is achieved by applying coatings techniques e.g. color, texture, mouth feel and taste masking, physical and chemical protection for the drugs in cores, and modified drug release characteristics all are achieved by coating the dosage forms. Aqueous or organic coating techniques are the most widely coating techniques in pharmaceutical industry. But these techniques have some disadvantages e.g. time consuming, stability for heat labile and hydrolysis of degradable drug and polluted environment problem. Thus, non-solvent coating is introduced as a substitute coating technique to overwhelm these disadvantages. Non-solvent coatings have been categorized as press coating, hot melt coating, supercritical fluid spray coating, electrostatic coating, dry powder coating and photo curable coating [10].

### 3.1 Compression Coating or Press Coating technique

Compression coating is also known as dry coating or press coating. It was one of the first solvent-free coating techniques. Typically, a compression-coated tablet comprises of an inner drug core and an outer coating shell. In this technique the inner core is completely enclosed by the outer layer. The material used in the outer layer controls and aids greatly to the tablet performance including mechanical strength of coated material, drug release pattern and also the drug stability [11].
Within the same dosage form compression coating technique permits the physical separation of incompatible drugs in the core tablet and the coat layer. Combination dosage forms can be produce in which different gastrointestinal tract areas are targeted with two separate active substances. Direct compression of the core tablet and the coat layer evade the requirement for a separate coating process. Compressibility of compression-coated tablets is highly reliant on the coating material. Conventionally, the compression-coating process comprises the compression of the core tablet, followed by the compression of core-coating material around the core tablet. The outer layer forming material is filled within the compression die and core tablet is placed over this material. The core is then surrounded with the outer layer-forming material and compressed with the powder and core inside it. One problem related with this method is the position of core tablet in the coating. Variations may exist if the core tablet is not positioned in the center of the compressed coated tablet and problems in the tablet performance may be seen [12].
Hariharan and Gupta (2002) produce compression-coated tablets by using an altered three-layer tablet press and simultaneously produced the core and coated tablets. They use the method in which double conjoined tablet press compresses the core tablet on one side and then this core tablet is transferred to the other side for coating process. The start of the coating process is with the formation of a cup-shaped outer layer comprising of the coating blend and then inclusion of drug or core materials and lastly another outer coating layer on the top. The core can be composed of pure drug crystals, drug-excipients blends, granules, microspheres, or beads. Poorly

compactable materials can also practically incorporate in the tablet core. In this case, on outer layer gives the required sufficiently compactable mechanical strength to the core tablet and the formulation [13].

The polymers can be used in the compression coating technique which can serve as a rate controlling hydrophilic membrane. Appropriate polymer blend can give controlled release of drug. In delayed release dosage forms Cellulose derivatives are often used as outer layer materials in dry coated tablets because they are gel-forming, water soluble material. These derivatives may include the following hydroxypropyl methylcellulose, hydroxymethyl cellulose, carboxymethylcellulose, and hydroxypropyl cellulose. The erosion of outer layer releases the drug in compression coating technique, therefore, the erosion rates of the outer layer and the speed of water penetration into the outer layer is important factor. By increasing the concentration of polymer in the coating blend or by increasing the layer thickness it is possible to obtain delayed release and/or sustained release effects. The sustained rate of release of core material can be controlled by incorporating polymer in the core with the drug [10].

The lag time before the drug release is controlled by Sawada and colleagues who formulated a compression-coated timed-release formulation containing nifedipine in the core tablet with different proportions of polyethylene oxide (PEO) and polyethylene glycol (PEG) mixtures in the coating to regulator the lag time before release. In this system, the erosion of the polyethylene oxide (PEO)/polyethylene oxide (PEG) shell controls the lag time before drug release (2.5–5.3 hr). The authors proposed to regulate morning surge in blood pressure with administration of such a system at bedtime [14].

A press coated tablet was formulated using sodium diclofenac compressed in the inner core and sucralfate in the outer shell. Non-steroidal anti-inflammatory drugs (NSAIDs) are recognized to directly damage gastro duodenal mucosa. To overcome this problem sucralfate was released from the coating before sodium diclofenac and a protective layer is formed to reduce the possibility for Non-steroidal anti-inflammatory drugs NSAID persuaded injury. Immediate or prolonged release core formulations were designed [10].

Direct compression with the advantages such as low equipment costs, short processing time and limited steps, low labor and energy requirements, and use of non-solvent processes is an established pharmaceutical manufacturing technique. Different solid dosage forms, such as fast-disintegrating tablets or controlled-release preparations are prepared by this method recently. In order to accomplish the chronopharmaceutical design for time-controlled release preparations, a TIMERx technology with an erosion mechanism was developed to achieve the chronotherapeutic delivery system [15].

Compression coated systems offers a numerous benefits over conventional coating methods when used for delaying and targeting drug moieties to the colon, these benefits includes short processing times, reduction in the equipment and labour costs, decreased energy expenditure and restriction of steps and solvents in the manufacturing process. Furthermore, compression coated systems are formulated using biodegradable polymers, which offer more benefits like ease of degradation by the colonic micro-flora and delayed, as well as site-specific, release in the colon [15].

### 3.1.1 Applications of compression coating (press coating) technique

To formulate incompatible drugs compression coating or press- coating became fascinating in the last two decades possessing certain advantages over liquid coating as this process does not need the use of solvents, requires a comparatively short manufacturing process and permits greater weight gain to the core tablet. In this day and age, pharmaceutical advantages of compression-coated tablets in dosage form development are:

*To protect hygroscopic, light-sensitive, oxygen labile or acid-labile drugs.*
*To separate incompatible drugs from each other and achieve sustained release.*
*To modify drug release pattern (delayed, pulsatile and programmable release for different drugs in one tablet).*

However, compression-coating technique also has some drawbacks e.g. the prerequisite of reliable and reproducible central positioning of the core tablet within compression-coated tablet, the need of a multiple-step process or a special tableting machine. Of late, the common manufacturing problems for compression-coated tablets, such as central positioning of the core in the compression-coated tablets and absence of core in coat, have been overwhelmed by applying a novel one-step dry coated tablet (OSDRC) method invented by Ozeki *et al*., (2004) [11].

### 3.2 Coat layer of compressed coated tablet

To improve drug performance, pharmacological effects and reduction of side effects the application of compressed polymeric coat on tablets for modified or controlled drug delivery systems have been developed and investigated. If the coated layer over the core tablet includes different properties of polymers, a variety of modified or controlled release can be obtained Based on the simplest matrix device where the drug is homogenously dispersed in the polymer network. The preparation development based on this concept can improve or adjust the drug release in a desired manner [16].

A fix dose drug combination including of telmisartan (angiotensin II receptor antagonist), ramipril (angiotensin converting enzyme) and optionally, a diuretic such as hydrochlorothiazide, was formulated in the form of an immediate release multilayer tablet. The multilayer tablet combined the features of pharmacological efficacy, adequate drug stability (due to the incompatibility between telmisartan and ramipril) and a robust manufacturing method was successfully prepared using compression coating technique [17].

The controlled release drug delivery systems can also be formulated using compression coating technique. Compression coating technique retards the release of soluble pH modifiers out of tablet cores, as compared to normal matrix tablet. In this case, compression-coated tablets, which enclosed a core of succinic acid as a pH modifier reservoir and a coat of dipyridamole, hydroxypropyl methylcellulose K100 (HPMC-K100) and succinic acid, could effectively upsurge the release of the weakly basic drug in higher pH medium by decreasing the microenvironment pH in the matrix coat [18].

A quick and slow biphasic release of ibuprofen from compression-coated tablets was prepared by Lopes and colleagues. Microcrystalline cellulose was used for the preparation of fast release layer of ibuprofen. Cellulose and sodium croscarmellose was used within ibuprofen extended release core [19].

A good in vitro/in vivo correlation was obtained from hydroxypropyl methylcellulose (HPMC) compression-coated tablets which contained one part of pseudoephedrine HCl in the cores and the other part of drug in the coats [20].

### 3.2.1 Inner core of compressed coated tablet

One of the pronounced approaches to achieving quick and slow drug release encompasses the use of a compressed core tablet system. The compressed core consists of a sustained release tablet, and a fast disintegrating formulation is coated by compression over the core tablet. Drug is present in both the core and the outer layer of compressed coating. From the viewpoint of manufacturing, it is difficult to formulate multilayer dosage forms because adhere additional layers together during pre-compression of multilayered tablets is a difficult procedure, this technology is an attractive alternative to the production of multilayer dosage forms. Additionally, because this system uses conventional manufacturing methods, it is more suitable to the industry [19].

To control the release of the drug (i.e., in the prolonged release component of the biphasic system) different polymers are used e.g. EC and HPMC may be used as sustained release agents in the core tablet. In matrix drug delivery systems, the release mechanism of the drug is fully dependent on the characteristics of the matrix-forming agent. HPMC due to its ability of swelling up and jellifying when in content with water is the most commonly used hydrophilic polymer among all others. A viscous layer is formed due to the gel formation, which acts as a protective barrier to both the invasion of water and the efflux of the drug in solution [21].

## 4. Mucoadhesion

Mucoadhesion or bioadhesion can be defined as the state in which interfacial forces maintain two materials together of which at least one is of biological nature for a prolonged time period [22]. This concept was applied to drug delivery system during the 1980s. It consists of the amalgamation of adhesive molecules into the pharmaceutical formulation anticipated to stay in close contact with the absorption tissue, releasing the drug near to the action site, thus increasing its bioavailability and promoting local and systemic effects [23].

Adhesion is defined as the state in which two materials, at least one biological in nature, are held together for an extended period of time by interfacial forces**.** It is also defined as the capability of a material (synthetic or biological) to stick to a biological tissue for an extended period of time. In case of mucoadhesion, the biological tissue involved is the mucous membrane. A succession of phenomena is required for mucoadhesion to occur. Firstly a close contact is require between a mucoadhesive polymer and a living membrane, this can be achieved either from good wetting of the mucoadhesive surface or from the swelling of the mucoadhesive substance. The second stage, starts after the contact is established between the mucoadhesive substance and the living membrane and penetration of the mucoadhesive into the fissure of the tissue surface or interpenetration of the chains of the mucoadhesive with those of the mucus takes place. Low chemical bonds can then settle .Mucoadhesive polymers are of both types i.e. water soluble and water insoluble polymers, which are swellable networks and joint by cross-linking agents. These polymers permit adequate wetting property by the mucus; possess optimal polarity and fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place. Mucoadhesive polymers that adhere to the musin epithelial surface can be suitably divided into three comprehensive classes:

*Polymers that become sticky when positioned in water and owe their mucoadhesion stickiness.*

*Polymers that adhere through general, non-covalent interactions that is principally electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).*

*Polymers that bind to specific receptor site on tile self-surface. All three polymer types can be used for drug delivery*

To achieve therapeutically effective drug concentrations in the systemic circulation and over extended periods of time controlled release drug delivery systems are designed, consequently achieving improved patient compliance and allowing a decrease of both the total dose of drug administered and the frequency of adverse side effects [24].

There are various approaches for controlled drug delivery. Among the numerous approaches used for controlled oral delivery of drugs, mucoadhesive drug delivery systems provide an effective substitute to the oral route of drug administration, to avoid first pass metabolism. Mucoadhesion is achieved by synthetic or natural polymers which interact with the mucus layer covering the mucosal membrane and covering the mucosal layer, the mucosal epithelial surface and mucin molecules set up a major portion of mucus [25].

### 4.1 Mechanism of mucoadhesion

The macromolecules mechanism of adhesion to the surface of a mucous tissue is not well understood yet. To initiate close contact and increase surface contact the mucoadhesive must spread over the substrate, endorsing the diffusion of its chains within the mucus. Both the attractive and repulsive forces will arise but for a mucoadhesive to be successfully adhering to the mucous the attraction forces must dominate. Dosage form nature and how the dosage form is administered facilitate each step of adhesion. For example, a partially hydrated polymer can be adsorbed by the substrate because of the attraction by the surface water [26].

The mechanism of mucoadhesion is in general divided in two steps i.e. the contact stage and the consolidation stage (Figure 1). The contact stage is considered as the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, presenting its deep contact with the mucus layer [27].

In ocular or vaginal formulations, the attachment of delivery system is by mechanical means over the membrane. In some other cases, the aerodynamics of the organ to which the system is administered promotes the deposition, such as for the nasal route. In the gastrointestinal tract it is not feasible to attach the formulation over the mucous membrane directly. Peristaltic motions can contribute to this contact, but there is little proof in the literature showing suitable adhesion.

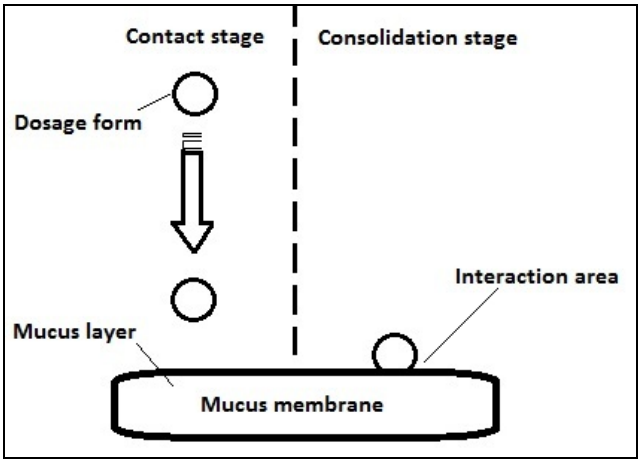


**Fig 1:** Mechanism of mucoadhesion

Moreover, in the esophagus an undesirable adhesion of the mucoadhesive dosage form can occur. Peristalsis explains the mucoadhesion in these cases and also the motion of organic fluids in the organ cavity, or by Brownian motion. If the particle leads to the mucous surface, it will come into contact with repulsive forces (osmotic pressure, electrostatic repulsion, etc.) and attractive forces (van der Waals forces and electrostatic attraction). Therefore, the particle must overwhelm this repulsive barrier [22].

In the consolidation step (Figure 1), the moisture present in the mucus membrane activates the mucoadhesive materials. The moisture present in the mucus membrane plasticize the system, permitting the mucoadhesive molecules to break free and to link up by weak van der Waals and hydrogen bonds [27].

Principally, there are two theories explaining the consolidation step one is the diffusion theory and the other is the dehydration theory. According to diffusion theory, the interpenetration of the chains of mucoadhesive molecules and the glycoproteins of the mucus mutually interact together and build secondary bonds [27]. This interaction only takes place when the mucoadhesive device has features favoring both chemical and mechanical interactions. For example, mucoadhesive properties can present by the molecules with hydrogen bonds building groups (–OH, –COOH), with an anionic surface charge, high molecular weight, flexible chains and surface-active properties, which induct its spread throughout the mucus layer [23].

According to dehydration theory, materials which readily jellify upon contact with an aqueous environment, when placed in contact with the mucus can cause dehydration of the mucus membrane due to the difference of osmotic pressure (Figure 2).

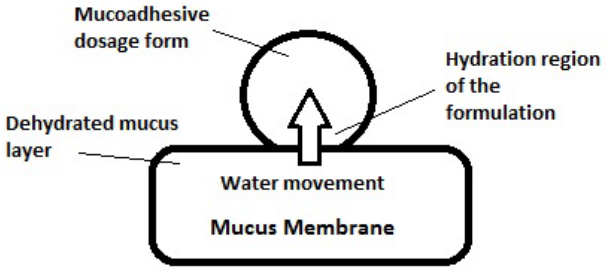


**Fig 2:** Mechanism of dehydration theory

The difference in concentration gradient due to osmotic pressure difference draws the water out of the mucus membrane into the formulation until the osmotic balance is reached. This process leads to the mixture of formulation and mucus and can consequently increases the contact time with the mucous membrane. Thus, consolidating the adhesive bond with the mucus membrane and it is the water motion that leads to this consolidation and not the interpenetration of macromolecular chains. Though, the dehydration theory is not applicable for solid formulations or highly hydrated forms [22].

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