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REVIEW ON THE FIXED DOSE COMBINATION DRUGS AND THEIR INCOMPATIBILITIES

Anand D. Savkare* and Rekha K. Wakhare

Department of Pharmaceutics, MVP Samaj's college of Pharmacy Nashik, Maharashtra, India.

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Correspondence to Author:

Anand D. Savkare

Assistant Professor (Pharmaceutics)
MVP Samaj's college of pharmacy,
Gangapur road, Shivajinagar,
Nashik - 422002, Maharashtra, India.


E-mail: wakharekha11@gmail.com

ABSTRACT: Incompatibility is an undesirable reaction that occurs between drugs, excipients, or with container. This may be therapeutic, chemical and physical incompatibility. Fixed dose combination provides challenge in product development due to incompatibility of two drugs. So severe degradation of drug in presence of each other. Formulation and stability difficulties arise with incompatible combination. It involves interaction between two or more substances (drug-drug, drug-excipients, drug-excipients-drug interactions) which leads to change in colour, odour, taste, viscosity, and morphology. There are various approaches to overcome incompatibility. Among which the bilayer tablet is one of the suitable approach and increasing attention from a variety of industries for various reasons *viz.* Therapeutic and marketing attendance with the great physical, chemical and microbial stability. The purpose of this review is to study the physical incompatibility between fixed dose combinations, to find remedies that overcome the problems in designing formulation and to select best optimised approach to reduce incompatibility issue in fixed dose combinations.

INTRODUCTION: **Incompatibility:** Drug Incompatibility refers to interactions between two or more substances which lead to changes in chemical, physical, therapeutic properties of the pharmaceutical dosage form.¹ In other words, Incompatibility is an undesirable result of mixing, prescribing and / or administering together two or more antagonistic substances which may affect safety, purpose or appearance of product.² The undesirable results may be the consequence of the interaction between formulation ingredients of the products formed due to these interaction.

Stability problems in combination products can be attributed to three types of interaction:

- **Drug–drug chemical interaction:** two or more drugs interact directly, resulting in drug degradation and a number of impurities; for example, lisinopril combined with aspirin undergoes acetylation to generate acetyl lisinopril, which could lead to a number of possible adverse events.
- **Drug–excipient interaction:** a drug in a combination product has an excipient that is incompatible with other drugs; for example, Telmisartan in a Telmisartan-hydrochlorothiazide combination product needs the incorporation of an alkaline excipient. Hydrochlorothiazide, however, degrades in an alkaline environment.
- **Drug–excipient–drug interaction:** occasionally, combination drugs, which may not be interacting directly, exhibit

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incompatibility in the presence of certain formulation components; for example, the combination of Rifampicin and Isoniazide is stable unless there is any excipient or agent that creates an acidic or alkaline environment.³

Types of incompatibility:

Incompatibilities are of three types:

1. Therapeutic incompatibility
2. Physical incompatibility
3. Chemical incompatibility

Physical incompatibility: Physical incompatibilities are often called pharmaceutical incompatibilities.

Definition: Interaction between two or more substances which lead to change in colour, odour, taste, viscosity and morphology.

Manifestations of physical incompatibility:

The following list outlines the various ways by which incompatibility between or among drug agents may be manifested.

1. Insolubility of prescribed agent in vehicle
2. Immiscibility of two or more liquids
3. Liquefaction of solids mixed in a dry state (called eutexia)

1. Insolubility: The following factors affect the solubility of prescribed agent in vehicle and may render it less soluble:

- A. Change in pH
- B. Milling
- C. Surfactant
- D. Chemical reaction
- E. Complex formation
- F. Co-solvent

Any change in previous factors may lead to precipitation of drugs and change in their properties.

2. Immiscibility of two or more liquids: This manifestation appears clearly in emulsion, creams, lotions, some types of ointments.

Separation in two phases is noticed in these pharmaceutical dosage forms. The following factors lead to immiscibility:

- A. Incomplete mixing

B. Addition of surfactant with:

- Unsuitable concentration
- False time of addition
- Unsuitable for the type of emulsion

C. Presence of microorganisms - Some bacteria grow on constituents of mixture *i.e.* gelatine, Arabic gum

- Others produce enzymes which oxidize the surfactant

D. Temperature Storage

- must be in room temperature to prevent separation

4. Liquefaction of solids mixed in a dry state (eutexia): It means that when two solid substances are mixed together, conversion to a liquid state take place.

It happens through the following methods:

1. Formation of liquid mixture: when the solid substance is soluble in another solid substance which leads to decrease of its melting point and conversion to a liquid in certain ratios.

2. Exit of crystalline water: By mixing hydrated crystals and dry crystals, crystalline water diffuse to dry crystals.²

Physical separation of the two drugs has been shown to be achieved in a number of Ways:

- ✓ Coating pellets of one active, before incorporating into a tablet of the other,
- ✓ Separately coating pellets of each active and then filling in a capsule,
- ✓ Coating pellets of one active and filling in a capsule with powder of the other active,
- ✓ Microencapsulating each active separately in order to ensure that the two drugs do not come in contact and then blending together for use in a tablet or capsule,
- ✓ Use of a dual or multiple compartment transdermal device, etc.
- ✓ By formulating bilayer tablet⁴

Some fixed dose combination drugs:

A] Amlodipine besylate and Benazepril hydrochloride:^{4,5}

Type of incompatibility: Physical

When Amlodipine and Benazepril are physically combined with each other formulation shows colour change from white to yellow colour.

Remedies:

1. Bilayer film: Bilayer formulations either as tablet or films (Buccal or fast dissolving oral films) is a need of time for successful development of Modified or Instant release formulation along with various features to provide successful drug delivery system. Bilayer formulations either as tablet or films (Buccal or fast dissolving oral films) can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles. Two incompatible drugs Amlodipine and Benazepril were combined in single dosage form using impermeable membrane. The thin films of both drugs were prepared by using different concentration of polymers, plasticizers and super disintegrants. The films were casted in to bilayer films using impermeable membrane. The drug release data reveals that the bioavailability was also increased which will reduce the dose and increased patient compliance. Hence it can be concluded that developed dosage form is better alternative dosage form for delivering two incompatible drugs and for acute cardiac conditions by increasing bioavailability of drugs and improves patient compliance.⁶

e. g. Amace-BP tablets

Manufacturer: Systopic Laboratories Pvt. Ltd
Usage: Blood Pressure, Cardiovascular, Hypertension
Active Ingredient: Amlodipine+Benazepril
Supplied Form: Tablet⁷

2. Capsule: capsule is best dosage form to avoid physical incompatibility between two drugs. Amlodipine besylate and Benazepril hydrochloride capsules are a combination of amlodipine besylate and Benazepril hydrochloride. The capsules are formulated in four different strengths for oral administration with a combination of amlodipine besylate equivalent to 2.5 mg, 5 mg or 10 mg of amlodipine, with 10 mg, 20 mg of Benazepril hydrochloride providing for the following available combinations: 2.5/10 mg, 5/10 mg, 5/20 mg and 10/20 mg. The inactive ingredients of the capsules are Crosspovidone, edible printing ink, gelatin, hydrophobic fumed silica, lactose anhydrous, magnesium stearate, microcrystalline cellulose, povidone, FD&C Blue #2 (present in 10/20 mg

strength), iron oxides, titanium dioxide (not present in 0/20 mg strength).^{8,9}

e.g. Lotrel

Manufacturer: Dr. Reddy's lab.
Usage: Blood Pressure, Cardiovascular, Hypertension
Active Ingredient: Amlodipine+Benazepril
Supplied Form: Capsule¹⁰

B] Amlodipine and losartan:

Incompatibility: Physical When amlodipine and losartan combined with each other, amlodipine may be locked inside of the formulation due to gelation of losartan in presence of amlodipine and formulation with simple mixing of two have very poor storage stability. To avoid such problem, they must be physically separated.¹¹

Remedies:

➤ **Bilayer tablets:** Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose also while the second layer is also designed to release the drug immediately. Bilayer tablet is suitable for sequential release of two drugs in combination and separate two incompatible substances. Losartan potassium & Amlodipine besylate are Anti hypertensive drugs. But when were combined by simple mixing and made a formulation, Losartan was showing the gelation property which reduced the dissolution capacity of a drug. So to overcome this problem, the formulation was made into bilayer tablet which maintain the dissolution constantly in the stomach at any pH value, which leads to constant release of the drug.¹²

Marketed solution:**a. Acord-L**

Usage: Hypertension
Active ingredients: Amlodipine 5 mg
Benazepril 50 mg
Manufacturer: Invision medi Pharma
Supplied form: Tablet

b. Actilop-AM

Usage: Hypertension

Active ingredient: Losartan potassium 50mg,
Amlodipine 5mg.

Manufacturer: Active healthcare

Supplied form: Tablet

c. Amlopres-Z

Usage: Hypertension

Active ingredient: Losartan potassium
Amlodipine

Manufacturer: Cipla limited

Supplied form: Tablet¹³

3. Telmisartan and Hydrochlorothiazide:

When telmisartan and hydrochlorothiazide combined with each other, hydrochlorothiazide unstable in alkaline condition and telmisartan need alkaline excipients for faster dissolution. Therefore there is need to separate two active ingredients in one dosage form.¹⁴

Remedies:

- **Bilayer tablet:** The purpose of this dosage form was to develop a stable formulation of Antihypertensive drugs of the Telmisartan and Hydrochlorothiazide immediate release bilayer tablet and to study the dissolution profile with the reference product. The Formulation development work was initiated with wet granulation (drug layering technique) as the APIs are very static in nature and having very poor flow property. In order to improve solubility and drug release, Telmisartan is converted to its sodium salt by dissolving in aqueous solution of Sodium Hydroxide. Lactose Monohydrate and Microcrystalline Cellulose are used as diluents. Sodium Starch Glycolate is added as a superdisintegrants and Magnesium Stearate is used as the lubricant. The prepared granules are compressed into Double layer compression machine. The tablets thus formulated showed satisfactory physical parameters, and it was found to be stable and in-vitro release studies are shown that formulation (A5B5) shows Cumulative percent drug release 98.9-103.7% within 60min and matches with that of Innovator.^{15,16}

Marketed solution:

a. A2B H

Usage: Hypertension

Active ingredients: Telmisartan,
Hydrochlorothiazide

Manufacturer: Fidelity Life sciences Pvt. Ltd

Supplied form: tablet

b. Adcom H

Usage: Hypertension

Active ingredient: Telmisartan,
Hydrochlorothiazide

Manufacturer: Intel pharmaceuticals

Supplied form: Tablet

c. Arbitel- H

Usage: Hypertension

Active ingredient: Telmisartan,
Hydrochlorothiazide

Manufacturer: Cardicare (micro lab Ltd)

Supplied form: Tablet

d. Astel-H

Usage: Hypertension

Active ingredients: Telmisartan,
hydrochlorothiazide

Manufacturer: AS Pharma

Supplied form: tablet¹⁷

e. Biotel40 –H

Usage: Hypertension

Active ingredient: Telmisartan,
Hydrochlorothiazide

Manufacturer: Biochemix Healthcare Pvt Ltd

Supplied form: Tablet¹⁸

4. Telmisartan and simvastatin:

Simvastatin is unstable in an alkaline condition while Telmisartan needs an alkaline ingredient for faster dissolution implying a monolithic tablet may be an unsuitable formulation, therefore need to separate these two active ingredient which results in low physical contact between them.¹⁹

Remedies:

- **Bilayer tablet:** A bilayer tablet comprises a first layer formulated for instant release of the angiotensin II receptor antagonist telmisartan from a dissolving tablet matrix and a second layer formulated for instant release of the HMG-CoA reductase inhibitor simvastatin from a disintegrating or eroding tablet matrix. The tablet according to the present invention provides a largely pH-independent dissolution of the poorly Water-soluble telmisartan, thereby

facilitating dissolution of the drug at a physiological pH level, and adequate stability and drug release of simvastatin. The tablet structure also overcomes the stability problem caused by the incompatibility of Simvastatin with basic constituents of Telmisartan.^{19, 20}

➤ **Gastroretentive Bilayer Floating Tablets:**

The gastroretentive bilayer floating tablets of Simvastatin as controlled release and Telmisartan as immediate release. The combination therapy of Telmisartan and Simvastatin is useful in serious cardiovascular adverse effect such as hypertension, congestive heart failure and exacerbation of angina which may occur along with increasing cholesterol level in the blood, while the fixed dose combination remain the preferable choice to the patient as compared to the individual dosage form. Bi-layer tablet is suitable for sequential release of two drugs in combination, two incompatible substances and also for controlled release of drug. The bilayer tablets are prepared using different super disintegrants like Sodium Starch Glycolate, Cross Carmellose Sodium, Crosspovidone for Telmisartan immediate release and xanthan gum, guar gum and HPMC K4M for Simvastatin controlled release. Sodium Bicarbonate is used as a gas generating agent. The pre-compression parameters like angle of repose, bulk density, tapped density; compressibility index and hausner's ratio were studied. The tablets were characterized by physical and chemical parameters such as tablet Uniformity of weight, thickness, hardness, diameter, friability, drug content, swelling index and In vitro drug release.²¹

5. Amodiaquine. HCl and Artesunate:

Fixed dose combination of artesunate & amodiaquine hydrochloride provided challenge in product development due to incompatibility of two drugs. So severe degradation of the drugs in presence of each other. The main issue was stability of artesunate in formulation. Artesunate causes degradation due to acidic nature of amodiaquine HCL.^{22, 23}

Artesunate is easily degraded by heat and aqueous conditions. The key factors for Artesunate degradation have been identified in pre-formulation

studies as the combination of humidity (> 1%w/w) and temperature ($\geq 40^{\circ}\text{C}$) on one hand (typically tropical conditions), and the presence of Amodiaquine (or another quinoline, *e.g.* quinine) and/or HCl.

To prevent Artesunate degradation several strategies were tried and many proved inadequate:

- Formulating Amodiaquine in the inner phase and Artesunate in the external phase of tablets.
- Reducing residual water presence in the tablets either through wet or dry granulation. For alcoholic wet granulation, handling 95% ethanolic solution at industrial scale was not possible. Replacing wet granulation by dry granulation (Amodiaquine powder was not suitable for direct compression) was not sufficient to ensure Artesunate stability and the addition of an hydrophobic agent (silicon dioxide) increased AS degradation, possibly through radical interaction.
- Manufacturing in controlled atmospheric conditions still led to > 5% AS tablet content loss after 3 months at $40^{\circ}\text{C}/75\% \text{RH}$.
- Adding a pH regulator (CaCO_3) improved partly AS stability but did not prevent degradation completely in dry granulation tablets even when combined with controlled atmospheric conditions manufacturing as some DHA was still detected.
- Controlled atmosphere conditions manufacturing did not meet cost requirements. Tablet protective coating was not considered as a suitable condition to avoid water contact.

Remedies:

- **Bilayer tablets :** The present investigation was to develop stable cost effective fixed dose combination moisture barrier film coated bilayer tablet of two incompatible drug artesunate and amodiaquine hydrochloride for improving patient adherence, compliance, convenience, reduce cost and improve stability of dosage form. Reduced pill burden, therapy period & effective treatment of multidrug resistance & falciparum malaria improved patient compliance, convenience. Results of Preformulation study indicated that it was necessary to develop formulation in humidity & temperature controlled environment. Artesunate

was very moisture sensitive drug so blend of artesunate layer was prepared by dry granulation method and blend of amodiaquine hydrochloride layer was prepared by wet granulation method. The formula of artesunate layer was optimized using factorial designs & using calcium carbonate as basic stabilizing agent.

The formula of amodiaquine hydrochloride was optimized using PVPK-30 as a binder. Coating parameters were optimized using factorial designs. Instamoistshield moisture barrier coating material was ready to use mixture of polymers, plasticizers, pigments, opacifiers and other excipients which could be used with organic or hydro-alcoholic systems for protection against atmospheric moisture. Result of present study suggested that stable artesunate and amodiaquine hydrochloride moisture barrier film coated bilayer tablet could be successfully formulated using calcium carbonate as basic stabilizing agent & instamoistshield as moisture barrier coating material.²²

e.g. a. Winthrop:

Usage: Anti-malarial

Active ingredients: Artesunate, Amodiaquine
100/270 mg

Supplied form: Tablet

Manufacturer: MAPHAR Laboratories

b. Tesquine:

Usage: Anti-malaria

Active ingredients: Artesunate 50mg, Amodiaquine
150mg

Manufactured by: Yanzhou xier kangtai
pharmaceutical co. Ltd

Supplied form: Tablet²⁴

c. Coarsucam:

Usage: Anti-malaria

Active ingredients: Artesunate, Amodiaquine
25 mg + 67.5 mg
50 mg + 135 mg
100 mg + 270 mg

Manufacturer: Sanofi-Aventis

Supplied form: Tablet^{25, 26}

6. Telmisartan and Amlodipine:

Amolodipine is unstable in alkaline excipients due to ester bonds in the amlodipine molecule appear subject to hydrolysis when exposed to an alkaline medium. A telmisartan formulation shows acceptable *in vivo* performance has to comprise basic components like, for example, sodium hydroxide or meglumine, so they are incompatible with each other.²⁷

Remedies:

➤ **Bilayer tablet:** Bilayer tablet system contains two layers containing two incompatible drugs each formulated in single layer. Such tablets are commonly used to avoid chemical incompatibilities of formulation components by physical separation. Bilayer release tablets can have

1) Both immediate release layers

2) Both sustained release layers.

3) One immediate release and one sustained release layer.

In this system both the layers are of immediate release pattern.

A bilayer tablet comprises a first layer formulated for instant release of the angiotensin II receptor antagonist Telmisartan from a dissolving tablet matrix and a second layer formulated for instant release of the calcium channel blocker amlodipine from a disintegrating or eroding tablet matrix.²⁸

e.g. a. Cortel –A

Usage: Hypertension

Active ingredients: Telmisartan, Amlodipine

Manufacturer: Corona Laboratories

Supplied form: Tablet²⁹

b. Twynsta®

Usage: Hypertension

Active ingredients: Telmisartan, amlodipine

Manufacturer: Boehringer Ingelheim
Pharmaceuticals Inc.

Supplied form: Tablet³⁰

c. Aritel-A

Usage: Hypertension

Active ingredients: Telmisartan, amlodipine

Manufacturer: Arian

Supplied form: Tablet²⁹

Best Optimised Approach: From above study we come to know that bilayer tablet is the most suitable approach to avoid physical and chemical incompatibility between drugs. Bi-layer tablets can be a primary option to avoid chemical incompatibilities between APIs by physical separation, and to enable the development of different drug release profiles (immediate release with extended release).³¹



FIG. 1: BILAYER TABLET³²

Goal to design bilayer tablets:

- Bilayer tablet is suitable for sequential release of two APIs which have different release profiles and physical incompatibilities. In this, the immediate release layer releases the drug immediately whereas the sustained release layer releases the drug in a controlled manner to maintain the therapeutic concentration for a prolonged period. This also acts as a maintenance dose.
- Control the delivery rate of either single or both the APIs by utilizing the functional property of the other.
- For the administration of fixed dose combinations of drugs, prolong the drug product life cycle, buccal/mucoadhesive delivery systems, manufacture novel drug delivery systems such as chewing devices and floating tablets for gastro-retentive drug delivery systems.
- To adapt the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for controlled release.

Challenges in bilayer manufacturing:

Conceptually, bilayer tablets can be seen as two single-layer tablets compressed into one. In practice, there are some manufacturing challenges.

Delamination: Tablet falls apart when the two halves of the tablet do not bond completely. The two granulations should adhere when compressed.

Cross-contamination: When the granulation of the first layer intermingles with the granulation of the second layer or vice versa, cross-contamination occurs. It may conquer the very purpose of the bilayer tablet. Proper dust collection goes a long way toward preventing cross-contamination.

Production yields: To prevent cross-contamination, dust collection is required which leads to losses. Thus, bilayer tablets have lower yields than single-layer tablets.

Cost: Bilayer tableting is more expensive than single layer tableting for several reasons. First, the tablet press costs more. Second, the press generally runs more slowly in bilayer mode. Third, development of two compatible granulations is a must, which means more time spent on formulation development, analysis and validation.³³

Advantages of the bilayer tablet dosage form:

1. Bi-layer execution with optional single-layer conversion kit.
2. Cost is lower compared to all other oral dosage forms.
3. Greatest chemical and microbial stability over all oral dosage forms.
4. Objectionable odour and bitter taste can be masked by coating technique.
5. Flexible Concept.
6. They are unit dosage forms and offer the greatest capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
7. Easy to swallow with least tendency for hang up.
8. Suitable for large scale production.³⁴

Disadvantages of bilayer tablet dosage form:

1. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.

2. Bitter tasting drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.
3. Difficult to swallow in case of children and unconscious patients.
4. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.^{33, 34}

Various approaches used in the bilayer tablet:

a) Floating Drug Delivery System: From the formulation and technological point of view, the floating drug delivery systems are considerably easy and logical approach in the development of Gastro retentive dosage forms (GRDFs).

Approaches to design Floating Drug Delivery System: The following approaches have been used for the design of floating dosage forms of single- and multiple-unit systems.

Intragastric bilayer floating tablets: These are also compressed tablet as shown in figure and contain two layers i.e. Immediate and sustained release

Multiple unit type floating pills: These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density.

b) Polymeric Bio adhesive System: These are designed to imbibe fluid following administration such that the outer layer becomes a viscous, tacky material that adheres to the gastric mucosa/mucus layer. This should encourage gastric retention until the adhesive forces are weakened. These are prepared as one layer with immediate dosing and other layer with bio adhesive property.

Disadvantages: The success is seen in animal models with such system has not been translated to human subjects due to differences in mucous amounts, consistency between animals and humans. The system adheres to mucous not

mucosa. The mucous layer in humans would appear to slough off readily, carrying any dosage form with it. Therefore, bio adhesive dosage form would not appear to offer solution for extended delivery of drug over a period of more than a few hours.

c) Swelling System: These are designed to be sufficiently small on administration so as not to make ingestion of the dosage form difficult (*e.g.*, less than approximately 23 mm long and less than 11 mm wide for an oval or capsule –shaped tablet whereas 10- 12mm in diameter for round tablets). On ingestion they rapidly swell or disintegrate or unfold to a size that precludes passage through the pylorus until after drug release has progressed to a required degree. Gradual erosion of the system or its breakdown into smaller particles enables it to leave stomach. The simple bilayer tablet may contain an immediate release layer with the other layer as extended release or conventional release.³¹

Applications:

1. Bi-layer tablet is suitable for sequential release of two drugs in combination
2. Separate Two Incompatible Substances.
3. Promoting Patient Convenience and Compliance.
4. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet
5. Bilayer tablets are used to deliver the loading dose and sustained dose of the same or different drugs.
6. Bilayer tablets are used for bilayer floating tablets in which one layer is floating layer another one is immediate release layer of the drug.
7. Bilayer tablets are used to deliver the two different drugs having different release profiles.³⁵

CONCLUSION: From above review it can be concluded that there are various drug combinations which are incompatible with each other needs to be separated in formulation to minimise the degradation therefore, bilayer tablet is novel approach to overcome incompatibilities between two drugs. Bilayer tablet is improved beneficial technology to overcome the shortcoming of two incompatible drugs. Because of ease of administration, patient compliance, economic

approach. Compared to all other oral dosage form it is widely accepted.

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