ORIGINAL ARTICLE

# Preparation and characterization of microspheres of ivabradine hydrochloride using natural, semi-synthetic, and synthetic polymers

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## Abstract

The present work was aimed to the development of controlled release formulations of esomeprazole and dexlansoprazole to improve bioavailability. Both esomeprazole and dexlansoprazole are the proton-pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell. By acting specifically on the proton pump, esomeprazole and dexlansoprazole block the final step in acid production, thus reducing gastric acidity.

**Key words:** Hydrochloride, ivabradine, microspheres, semi-synthetic, synthetic polymers

## INTRODUCTION

### Oral Drug Delivery System

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to acquire quick and entire systemic drug absorption.

A modified-release dosage form is defined "as one for which the drug release characteristics of time course and/or location are preferred to achieve therapeutic or convenience objectives not accessible by conventional dosage forms such as solutions, ointments, or punctually dissolving dosage forms as presently recognized." Several types of modified-release drug products are recognized[1]:

#### *Extended-release drug products*

A dosage form that allows at least a 2-fold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release, and long-acting drug products.

#### *Delayed-release drug products*

A dosage form releases a discrete portion or portions of drug, at a time or at times other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products.

#### *Targeted release drug products*

A dosage form releases drug at or near the intended physiologic site of action. Targeted release dosage forms may have either immediate-/extended-release characteristics.[2]

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Modified-release drug products are considered for altered routes of administration based on the physicochemical, pharmacologic, and PK properties of the drug and on the properties of the materials used in the dosage form. Numerous unlike terms are now defined to describe the available types of modified-release drug products based on the drug release characteristics of the products.[3]

## Oral Controlled Release Drug Delivery Systems

Oral ingestion is conventionally chosen route of drug administration, provided that an expedient method of effectively achieve both local and systemic effects. In conventional oral drug delivery systems, there is very little control over release of drug.

An ideal odd has to steadily deliver an assessable and reproducible amount of drug to the target site over a prolonged period. CR delivery system provides a consistent concentration or amount of the drug at the absorption site and, therefore, after absorption allow maintenance of plasma concentrations within a therapeutic range, which diminish side effects and also decrease the frequency of administration.

To conquer the drawbacks of CDDS, numerous technical progressions have led to the expansion of CDDS that could modernize method of medication and afford a number of therapeutic benefits.[4]

## Types of Oral Controlled Release Drug Delivery Systems:[5,6]

A number of techniques are used to achieve controlled release of drugs through the oral cavity. The majority of the oral controlled release systems relay on dissolution, diffusion, or a combination of both mechanisms to generate slow release of drug.

- Dissolution controlled release systems.
- Diffusion controlled release systems.
- Diffusion and dissolution systems.
- Osmotically controlled release systems.
- Gastroretentive drug delivery systems.
- Electrically stimulated

## Dissolution Controlled Release Systems

A drug with a slow dissolution rate will sustain release rate of the drug from the dosage form. Here, the rate-limiting step is dissolution. This being true, sustained release preparation of drugs could be made by decreasing their rate of dissolution.

Dissolution controlled systems can be made either by

- Varying concentration of rate controlling coats or polymers (Matrix Dissolution Systems).
- By administering the drug as a group of beads that have coating of different thickness (Encapsulated Dissolution Systems).

## Diffusion Controlled Release Systems

In these systems, the release rate of drug is determined by its diffusion through a water insoluble polymer. There are basically two types of diffusion devices.

- Reservoir devices (The methods used to develop reservoir type devices include microencapsulation of drug particles and coating of tablets containing drug cores).
- Matrix devices (The most common method of preparation is to mix the drug with the matrix material and then compress the mixture).

## Osmotically Controlled Release Systems

The osmotic pump represents a newer concept in extended-release preparations. Drug delivery is controlled by the use of an osmotically controlled device. A representative osmotic oral drug product is the "push-pull" system called Gastrointestinal Therapeutic System (GITS), developed by Alza Corporation for nifedipine (Procardia XL) and other drugs. The system consists of a semipermeable membrane and a two-layer core of osmotic ingredient and active drug. As water enters the system, the osmotic pressure builds up from the inner layer, pushing the drug out through a laser-drilled orifice in the drug layer.

## Gastroretentive Drug Delivery Systems

Dosage forms that can be retained in stomach are called Gastroretentive Drug Delivery Systems (GRDDSs). GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site thus ensuring its optimal bioavailability.

The approaches that have been pursued to increase the retention of an oral dosage form in the stomach include bioadhesive systems [Tables 1 and 2] (The bioadhesives increase the residence time and contact time at the area of absorption and provide a high concentration gradient across the membrane), swelling and expanding systems (it incorporate hydrogels which are polymers that can swell up to 100 times their dry weight), and high-density systems and low-density (floating) systems (suitable for drugs that are poorly soluble or unstable in the intestinal medium).

**Table 1:** Modified drug deliveries

| Route of administration | Drug product | Examples | Comments |
|---|---|---|---|
| Oral drug products | Extended release | Diltiazem HCl extended release | Once-a-day dosing |
| | Delayed release | Mesalamine delayed release | Coated for drug release in terminal ileum |
| | Oral mucosal drug delivery | Oral transmucosal fentanyl citrate | Fentanyl citrate is in the form of a flavored sugar lozenge that dissolves slowly in the mouth |
| Ophthalmic drug delivery | Insert | Controlled release pilocarpine | Elliptically shaped insert designed for continuous release of pilocarpine following place mention the cul-de-sac of the eye |
| Parenteral drug delivery | Intramuscular drug products | Depot injections | Lyophilized microspheres Containing leuprolide acetate for depot suspension |
| | | Water immiscible injections | Medroxyprogesterone acetate (Depo-Provera®) |
| | Subcutaneous drug products | Controlled release insulin | Basulin is a controlled-release, recombinant human insulin delivery |
| Transdermal drug delivery systems | Transdermal therapeutic system (TTS) | Clonidine transdermal therapeutic system | Clonidine TTS is applied every 7 days to intact skin on the upper arm or chest |
| | Iontophoretic drug delivery | | Small electric current moves charged molecules across the skin |

**Table 2:** Compositions of esomeprazole CR tablets (F1-F9)

| S. No. | Ingredients (mg/tab) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Esomeprazole | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| 2 | Eudragit S-100 | 20 | 40 | --- | --- | --- | --- | 20 | 20 | --- |
| 3 | Eudragit L-100 | --- | --- | 20 | 40 | --- | --- | 20 | --- | 20 |
| 4 | Eudragit RSPO | --- | --- | --- | --- | 20 | 40 | --- | --- | 20 |
| 5 | Talc | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 6 | Magnesium stearate | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | Dicalcium phosphate | Q.s | Q.s | Q.s | Q.s | Q.s | Q.s | Q.s | Q.s | Q.s |
| | Total weight | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

### Electrically Stimulated Release Device

These are monolithic devices prepared using polyelectrolyte gels which swell when an external electrical stimulus is applied, causing a change in pH.

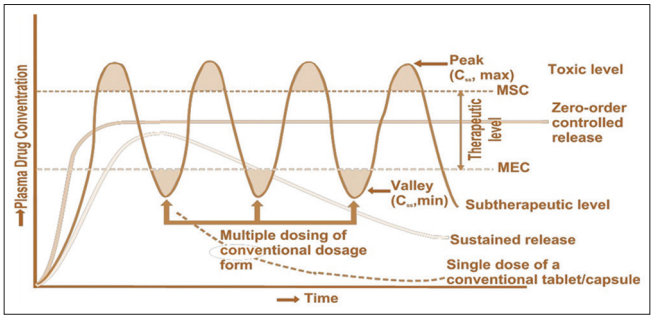



**Figure 1:** Conventional multiple dosing and single dosage of sustained and controlled delivery formulations of esomeprazole

## FORMULATION DEVELOPMENT OF TABLETS

### Direct Compression Method

Different tablet formulations were prepared by direct compression technique. All powders were passed through 60 mesh. Required quantities of drug and polymers were mixed thoroughly magnesium stearate was added

as lubricant. Talc was used as glidant. Microcrystalline cellulose was used as diluent. Finally, the powder mix was subjected to compression after mixing uniformly in a polybag. Before compression, the blends were evaluated for several tests [Figure 1].

## DEXLANSOPRAZOLE COMPOSITIONS

### Evaluation of Post-Compression Parameters for Prepared Tablets

The designed formulation compression tablets were studied for their physicochemical properties such as weight variation, hardness, thickness, friability, and drug content.

### Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first-order, Higuchi, and Korsmeyer–Peppas release model.

### Stability Studies

The goal of formulation development is to determine a composition for the final dosage form that results in a safe, efficacious product which remains stable over the course of its intended use.[7-22]

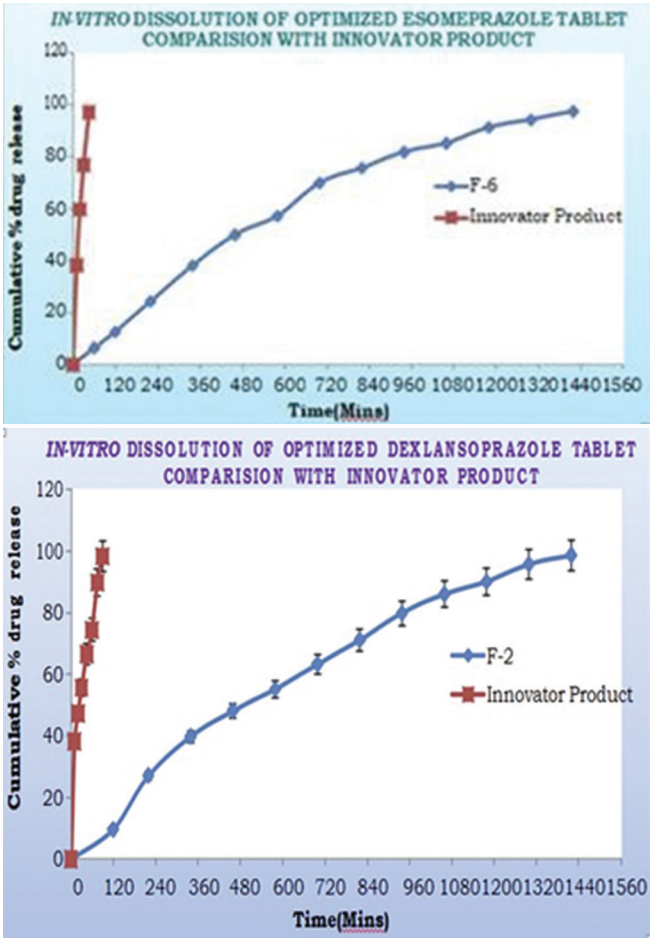
Under the influence of a variety of environmental factors such as temperature, humidity, and light enabling recommended storage conditions, retest periods and shelf lives.

## EXPERIMENTAL RESULTS AND DISCUSSION

### Results and Discussion of Dexlansoprazole

#### *In vitro drug release studies of esomeprazole and dexlansoprazole*

Based on *in vitro* release studies, it was clearly manifest that the drug release from finalized controlled release tablet dosage form has been prolonged for 24 h, whereas marketed Innovator product has shown almost complete cumulative % drug release in 45 min for esomeprazole and in 90 min for dexlansoprazole [Table 3]. Based on the results, it can be concluded that the innovator product needs to be administered 2–3 times in a day, while the esomeprazole CR tablet and dexlansoprazole controlled release tablet can be administered once daily is sufficient to continue the therapeutic concentration.




Comparison of *in vitro* drug release studies of optimized formulation of esomeprazole and dexlansoprazole CR with innovator product

### Stability Studies

#### *Stability studies of dexlansoprazole optimized formulation and esomeprazole optimized formulation*

Accelerated stability studies of optimized formulation were performed for a period of 6 months as per the ICH guidelines. No major segregation was initiated between evaluated parameters before and after storage and all are in acceptable limits. The tablets showed satisfactory at accelerated temperature 400°C ± 20°C/75% RH ± 5%.

## CONCLUSION

The current research work envisaged was an attempt to the development of controlled release formulations of esomeprazole and dexlansoprazole to improve bioavailability.

**Table 3:** Compositions of dexlansoprazole CR tablets (F1-F12)

| S. No. | Ingredients (mg/tab) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Dexlansoprazole | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| 2 | Carbopol-974 P | 150 | 75 | 50 | 100 | 75 | 50 | 100 | 20 | --- | --- | --- | --- |
| 3 | HPMC K4M | --- | 75 | 100 | 50 | --- | --- | --- | 150 | --- | --- | --- | --- |
| 4 | HPMC K 15M | --- | --- | --- | --- | 75 | 100 | 50 | --- | 150 | 75 | 50 | 100 |
| 5 | Sodium CMC | --- | --- | --- | --- | --- | --- | --- | --- | --- | 75 | 100 | 50 |
| 6 | Magnesium stearate | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 7 | Aerosil | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 8 | MCC | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 |
| | Total weight | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |

## ESOMEPRAZOLE

Esomeprazole is a proton-pump inhibitor used to treat gastroesophageal reflux disease (GERD). It is a short biological half-life (1–1.5 h), poor bioavailability (50–68%), and narrow therapeutic index. Since of all these parameters, esomeprazole was chosen as a good candidate for controlled drug delivery systems.

- Pre-formulation studies were performing for esomeprazole to recognize the drug excipients interactions using FTIR and DSC studies, showed that excipient was compatible.
- Esomeprazole controlled release tablets were formulated by direct compression method by distinct polymethacrylates such as Eudragit-S100, Eudragit -L100, Eudragit-RSPO, Eudragit-RS100, Eudragit-RL100, and Eudragit-RLPO.
- To prepare the different controlled release formulations of esomeprazole tablets with different polymers such as polymethacrylates such as Eudragit-S100, L-100, RSPO, RS-100, RL-100, RLPO, and talc is glidant, magnesium stearate is lubricant, and dicalcium phosphate was used as diluents by direct compression method.
- Esomeprazole formulated tablet blend and tablets were subjected to their pre- and post-formulation characteristics such as flow properties and weight variation, hardness, friability, and drug content. Results of all these parameters were within the pharmacopoeial limits.
- Developed formulations are deliberate for *in vitro* dissolution and release kinetic studies. Based on the results, F-6 formulation was chosen as a superlative among all the formulations in the point of drug release and mechanism. This formulation was kept for stability study for period of 6 months according to the ICH guidelines, results were conformed the optimized one is stable.

## DEXLANSOPRAZOLE

Dexlansoprazole is a proton-pump inhibitor used to treat heartburn caused by gastroesophageal reflux disease (GERD) and to heal erosive esophagitis (damage to the esophagus from stomach acid). It is a short biological half-life (1–2 h), bioavailability (60%), and narrow therapeutic index. Because of all these parameters, dexlansoprazole was preferred as a good aspirant for controlled drug delivery systems.

- Pre-formulation studies were executed for dexlansoprazole with polymers used were initiate comparable as per FTIR and DSC study interpretation.
- Using direct compression method, dexlansoprazole controlled release tablets were formulated with contradictory polymers such as acrylic acid polymer such as Carbopol-974P, HPMC grades for prevalence HPMC -K4M, HPMC-K15M, HPMC-K100M, natural polymers akin to xanthan gum, guar gum, sodium CMC, and pectin.
- Prepared formulations were evaluated for different physicochemical properties resembling pre- and post-compression parameters. Results were concluded that values were within the pharmacopoeial limits, then, these formulations were evaluated for *in vitro* drug release and kinetics and mechanism of drug release.
- Based on *in vitro* dissolution studies and release kinetics, F-2 formulation was preferred as an optimized among the all. This optimized formulation was compared with the innovator product; results showed increase the release profile.
- Stability studies were performed for optimized formulation F-2 for 6 months according to the ICH guidelines and found to be stable.

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