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A REVIEW- THE CURRENT SCENARIO OF EXPANDABLE DOSAGE FORM: A NOVELTY IN GASTRORETENTIVE DRUG DELIVERY SYSTEMS

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ABSTRACT

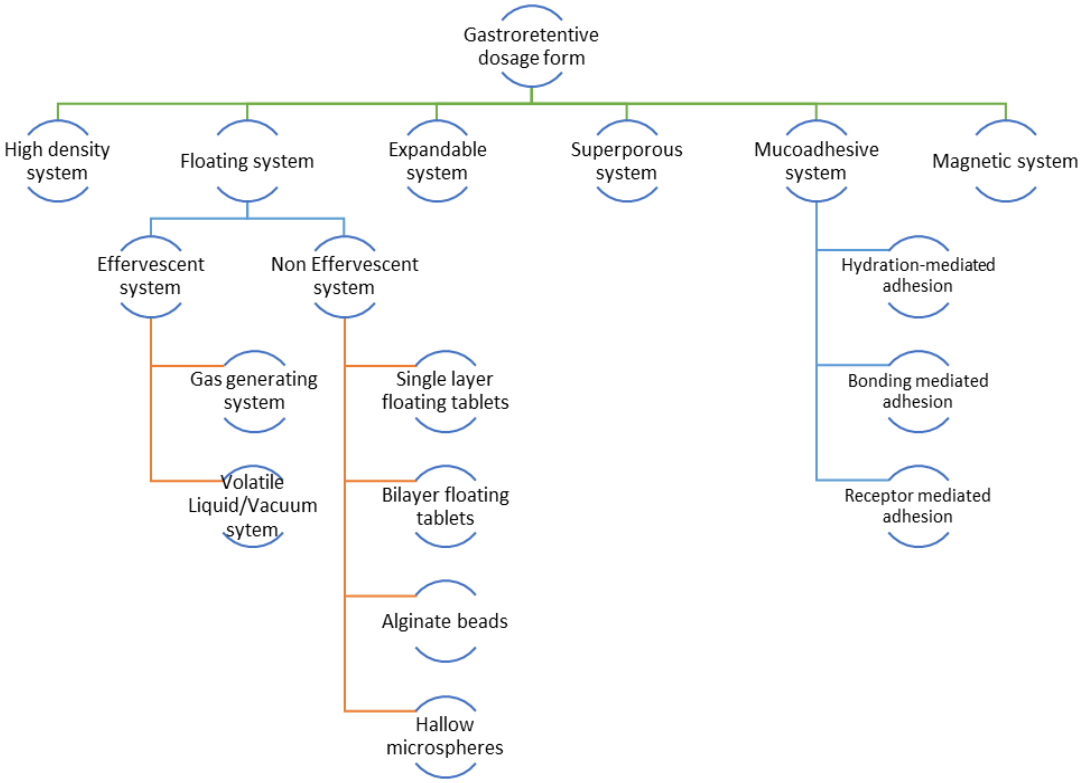
The purpose of this review is to understand the recent literature in the development of expandable drug delivery systems in order to achieve prolonged gastric retention. This review gives the brief about pros and cons of the expandable drug delivery system with the other oral conventional dosage and compares them. This review summarizes about the polymers used, preparation methods, mechanism of drug release and also the methods used to evaluate these systems by *In vitro* techniques. A special mention is given to the recent marketed and patented products in this review. These systems are the stepping stones for the future development of the pharmaceutical drug delivery systems.

INTRODUCTION

Oral formulations are significant among the various dosage forms developed for human administration. Conventional oral drug delivery provides a specific drug concentration in the systematic circulation with limited control drug delivery but limited in retention of dosage form in the stomach. However, the recent technological development has resulted to many novel pharmaceutical products, mainly the controlled drug delivery systems to overcome this problem. The prolonged residence dosage form in the stomach, called gastro retention, have various therapeutic and biopharmaceutical benefits. Some of the benefits are decreased fluctuations of drug concentration in the plasma, improved patient compliance due to reduced dosing frequency, improved local drug activity in the stomach and improved bioavailability of certain drugs with absorption window in the upper small intestine.[1] Gastroretentive drug

delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract for local or systemic effects.[2] Gastroretentive dosage forms can remain in the gastric region for long period and significantly prolong the gastric retention time of drugs. [3] This technology has generated enormous attention over the last few decades owing to its potential application to improve the oral delivery of some important drugs for which prolonged retention in the upper GI tract can greatly improve their oral bioavailability and their therapeutic outcome. There are several approaches of gastric retentive drug delivery being designed and developed includes:[2]

Classification



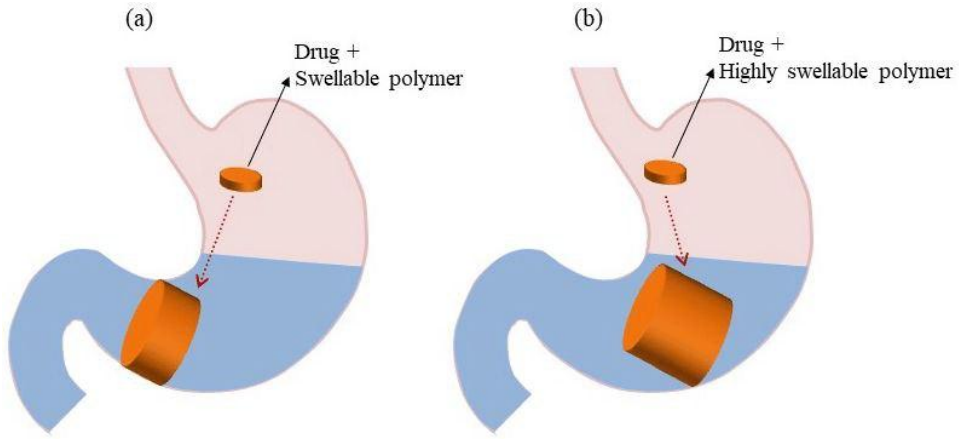
Expandable dosage forms are capable of expanding and retaining in the stomach for longer period. This dosage form in the stomach will be able to withstand gastric transit if it bigger than pyloric sphincter. However, the dosage form must be small enough to be swallowed and must not cause gastric obstruction either singly or by accumulation. There are some configurations required to develop an expandable system to prolong gastric retention time. It includes

I. A small configuration for oral intake
II. An expanded gastro retentive form

III. A final small form enabling evacuation following drug release from the device

The expansion can be achieved by swelling or by unfolding in the stomach. Swelling usually occurs due to osmosis. Unfolding takes place due to mechanical shape memory, i.e. the GRDF is fabricated in a large size and is folded into a pharmaceutical carrier e.g. a gelatin capsule, for convenient intake.[2]

Gastric retention is achieved due to the unfolding of the dosage form in the stomach within the 15 minutes of administration in case of folding type of expandable delivery systems. It provides drug release up to 12hrs in acidic medium. Expandable films are made up of biodegradable polymers such as HPMC, chitosan, acrylic acid derivatives etc. Klausner et. al initiated the research on expandable gastro retentive dosage form investigated on Riboflavin and levodopa expandable GRDF. Recently Intec pharma developed an expandable GRDF Accordion Pill Carbidopa/levodopa for the Parkinson's disease.[4]



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Advantages of Expandable dosage form

- ✓ Bioavailability is improved
- ✓ Dose frequency can be reduced
- ✓ Drug wastage can be prevented
- ✓ Therapeutic efficiency can be observed
- ✓ Solubility of less soluble drugs is improved
- ✓ Constant therapeutic levels are maintained over prolonged period
- ✓ It maintains sufficient size integrity and rigidity throughout the time period under gastric physiology
- ✓ Drugs with narrow absorption window can be used in this system.

Disadvantages of Expandable dosage form

- Drugs that get absorbed in colon are not suitable for this type of delivery system
- Expandable dosage system must not be interfering with gastric motility and be easily biodegradable. Storing of these biodegradable polymers used in it are difficult.
- Permanent retention of this large single unit dosage form may cause bowel obstruction, intestinal adhesion
- These dosage forms are difficult to industrialize
- These dosage forms are not cost effective

Comparison between expandable dosage form and oral conventional dosage form[6]

Parameters	**Expandable gastro retentive dosage form**	**Conventional drug delivery system**
Risk of toxicity	Lower	higher
Patient compliance	High compliance level	Less compliance level
Drug having low absorption in small intestine	appropriate	Not Appropriate
Drugs acting locally in stomach	Much useful	Not very much useful
Dose dumping	No risk	Risk of dose dumping is higher
Drugs with poor solubility at higher pH	Much beneficial	Not much beneficial
Drugs that have fast GIT absorption	Much beneficial	Not much beneficial
Drugs that undergo degradation in colon	Much beneficial	Not much beneficial
Bioavailability	high	low
Drug efficacy and therapeutic effect	high	low
dose	Single dose	Multiple dose

Composition of expandable dosage form

SL.NO	**INGREDIENTS**
1.	Active Ingredient
2.	Polymers
3.	Solvents
4.	Plasticizer

Polymers used in the expandable dosage form

There are mainly three types of polymers are used in formulation, it may be naturally occurring or synthetic or semi-synthetic. Naturally polymers are advantageous over synthetic polymers.

Advantages of natural polymers:

- Low cost
- Biocompatible
- Local availability
- Non toxic
- Environment friendly
- Biodegradable

Disadvantages of natural polymer:

- Microbial contamination
- Reduced viscosity on storage
- Extraction process very complicated and high cost
- High degree of variability
- Uncontrolled rate of hydration

Natural polymers

Chitosan: Chitosan is a natural swellable polymer and is a N-deacetylate derivative of chitin. Chitosan plays an important role in stomach-specific drug delivery, intestinal delivery and it is used as viscosity enhancer, mucoadhesive, disintegrant, coating agent, binders. It is water soluble and not soluble in inorganic solvents.

Guar gum: It is a natural non-toxic polysaccharide derived from seeds cymopsis tetragonolobus. It is used as binder, disintegrant, polymer in solid dosage form. It is water soluble and not soluble in inorganic solvents.

Xanthum gum: It is well known bipolymer which is natural, biosynthetic and an edible gum. It consists of glucose, mannose and glucuronic acid. It is used as a gelling agent, stabilizing agent, viscosity increasing agent, suspending agent, thickening agent and emulsifying agent.

Semi-synthetic/synthetic polymers

HPMC: HPMC acts as a binder, emulsifying agent and thickening agent. These are widely used in the oral, ophthalmic, nasal and topical formulation. It is a hydrophilic polymer which in contact with liquid swell and make a gel layer around dry core of polymer matrix.

Acrylic acid derivatives: These are the derivatives of acrylic acid methacrylic acid. It is available in different grades like Eudragit RL and RS, E and RS. RL and RS 100 are granular form and widely used and have mucoadhesive and pH independent swelling polymer. RS and RL grades contains quaternary amino groups and are used for sustained release formulation.

Ethyl cellulose: It is a long-chain polymer of b-anhydro glucose units joined together by ether linkage. It is used as binder, coating agent, viscosity enhancer.[1]

Methods to formulate expandable dosage form

Solvent Casting Technique

Ratio of all ingredients including drug, polymers and excipients are weighed accurately. The film is prepared by solvent casting method. Drug is added in mixture of solvent and a plasticizer. The prepared drug solution is then add together in the aqueous polymer solution followed by constant stirring. The resultant mixture is poured in the petri dish and is allowed to dry at room temperature for 48 hours. After drying, the films are removed using a sharp blade. The peeled films are then cut in required dimensions.[7]

Solvent Evaporation Technique

The polymeric films are prepared by Solvent Evaporation Technique. A polymeric dispersion was prepared by dissolving the polymers in the optimum quantity of solvents. The measured quantity of drug is added and dissolved well. It is then introduced into the polymeric mixture. Finally, plasticizer is added to this polymeric dispersion and stirred vigorously to obtain the uniform dispersion. The obtained drug polymer mixtures are poured into petri dish. It is allowed to dry for 24 hours at room temperature. The film thus obtained are carefully removed and are cut in required dimensions.[3]

Mechanism of drug release from expandable films

The expandable film is folded in the zigzag manner and insert into the hard gelatin capsule. Expansion of the film takes place once it comes into contact with gastric fluid. The films expand to a dimensions greater than pyloric sphincter upon contact with gastric fluids. It acts like plug, thus prevents from being evacuated by gastric emptying. It also ensures mechanical resistance to evacuation from stomach to the intestine. This helps to prolong the gastric residence time.[8]

Evaluation of expandable films

1. Weight variation:

Weight variation test is conducted for 10 films. The films are weighed individually. The average weights and standard deviations are calculated.[9]

2. Thickness variation test

The thickness of the films are measured using digital screw gauge. The mean ± SD values are calculated for all the formulations.[4]

The film thickness can also be determined by optimal microscopy by taking transverse section and observing under 100x magnification. The mean ± SD values are calculated.[9]

3. Folding endurance

The number of times of a film can be folded at a same place till it is broken gives the value of folding endurance. With this test, toughness of the film can be known. Lower the value of endurance specifies the brittleness of film.[7]

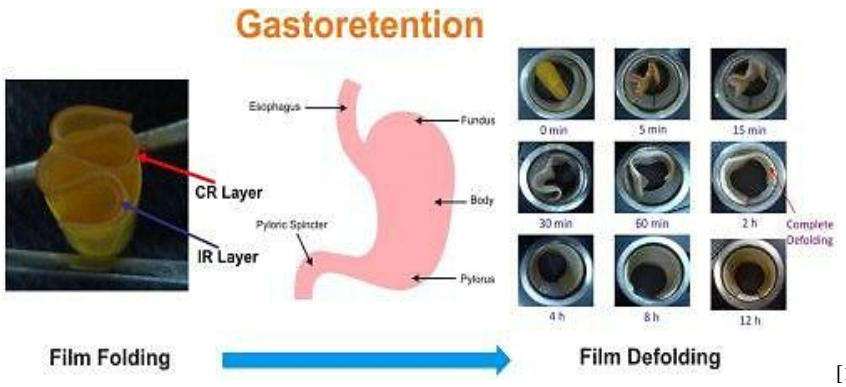
4. Swelling behavior

Initial weight of the film is recorded. Then the film is immersed in the buffer solution of 0.1 N HCl which is maintained at 37±0.5 ℃. After 120 minutes, the weight of film is recorded. Swelling index was calculated using following formula

$$\text{Swelling index (\%)} = (W_2\text{-}W_1)/W_1 * 100$$

5. Unfolding study

The Drug loaded films can be folded in 2 forms: Rolling or zig zag folding. Films are folded in either one of the manner and inserted in the capsule. In vitro unfolding test is carried out using 500 ml beaker filled with 0.1 N HCl. The folded drug loaded films are introduced into the beaker. At various interval of time, unfolding behavior of films are noticed.



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6. In vitro buoyancy studies

The floating behavior of the film is observed in this test. The capsules are placed in the beaker container 250 ml of 0.1N HCl. Constant stirring of 50 rpm speed is provided. The time taken for the floating and expansion is noticed by visual observation.[7]

7. Moisture content

The prepared films are weighed individually and kept in desiccator comprising calcium chloride at room temperature for 24 hours. After specified interval of time, the films are weighed until constant weight is observed. The percentage moisture content is calculated.[7]

% Moisture Content = [Initial weight – Final weight/ Final weight] *100

8. Drug content

Film is cut into pieces and out in 100 ml of buffer solution for complete extraction of drug. Solution is stirred continuously. Sample is withdrawn after specific period of time. Then the withdrawn sample is dilute with the buffer solution. With the help UV Vis spectroscopy set at λ_{max} of the drug, the drug content is determined.[7]

9. In vitro dissolution studies

In vitro drug release is studied using USP dissolution apparatus at 37 ± 0.5℃ in 900 ml of 0.1N HCl buffer solution with 50 rpm speed. The prepared films are immersed in the dissolution medium. An aliquot of 5ml is withdrawn and replaced with 5ml fresh buffer solution at various intervals of time. The content of the drug is analyzed using UV-Vis spectroscopy at λmax.[3]

10. Scanning Electron microscopy

The morphology of the polymeric film is scanned using Scanning Electron Microscopy. The drug loaded polymeric films morphology is studies in different magnifications. Scanning electron microscopy analysis provides high resolution imaging useful for evaluating various materials for surface fractures, flaws, contaminants. And it can produce images that can show information on a materials surface composition and tolography. SEM is also capable of performing analysis of selected point locations on the sample.

11. FT-IR spectroscopic studies

FT-IR studies helps in identification of organic molecular groups, functional groups, side chains and cross links involved. Chemical interaction between drug and polymer can be

understood in this study. FTIR of pure drug, physical mixture and polymeric film are estimated in terms of vibrational frequencies in the infrared range. The scanning range is 4000-400 cm^{-1}.

12. Differential Scanning Calorimetry

Differential Scanning Calorimetry is used to study the thermal analysis of drug-excipient compatibility. The DSC thermogram of pure drug, solid dispersion of physical mixture and polymeric film is estimated in terms of their endotherms using DSC. The samples are heated from 30 to 300℃ at heating rate of 10℃/minute under nitrogen atmosphere.[3]

13. X-Ray Diffraction studies

X-Ray diffraction studies were carried out to reveal the crystalline modifications during the preparation of films.

Marketed expandable films

SL.NO	BRAND NAME	MANUFACTURER /DISTRIBUTOR	API	USES
1.	Accordion pill	Intec Pharma	Carbidopa/Levodopa	Treatment of Parkinsonism disease

Current patents on expandable dosage form

CA2143500A1 - Expandable pharmaceutical forms - Google Patents

https://patents.google.com/patent/CA2143500A1/en

EP3148514A4 - Expandable gastroretentive dosage form - Google Patents

https://patents.google.com/patent/EP3148514A4/en

US10737079B2 - Gastric residence system - Google Patents

https://patents.google.com/patent/US10737079B2/en?inventor=Ilan+Zalit

CONCLUSION

For the drug to show its action, drug absorption in the gastrointestinal tract is very important which can be achieved through expandable drug delivery systems. Expandable dosage forms are the recent developments for the poorly absorbed drug to accomplish the goal of prolonged gastric retention. Although these systems have disadvantages but it can still be worked out to achieve even better pharmaceutical products for the future days.

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