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Review Article

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A Review On innovative approach for the management of pain with GI protection.

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Keywords

Chrono-therapeutics;
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Misoprostol;
Pain.

Abstract

The most convenient and commonly employed route of drug delivery has been by oral ingestion. Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. It is considered as the most natural, uncomplicated, convenient and safe route. Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. They can be mass produced with robust quality controls and offer different branding possibilities by means of colored film coating, different shapes, sizes or logos.

Capsules are solid dosage forms in which drug is enclosed within either a hard or soft soluble shell. To formulate a combination dosage form of Aceclofenac Extended Release Tablet200 mg and Misoprostol Immediate Release Tablet 200 mcg enclosed in Size '0' elongated Hard Gelatin Capsules. A Tablet in Capsule device containing Aceclofenac ER tablet and Misoprostol IR tablet for Pain Management with Gastro protection was formulated. Rationale of combining a NSAID and a prostaglandin analogue was well justified and the design of drug delivery system was made simple by encapsulating two different tablets (Aceclofenac and Misoprostol) in single capsule and it offers advantage in terms of GI protection, Patient Compliance and Chrono-therapeutics.

Introduction

Historically, the most convenient and commonly employed route of drug delivery has been by oral ingestion.[1] Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. It is considered as the most natural, uncomplicated, convenient and safe route.[2]

Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. They are the most widely preferred form of medication both by pharmaceutical manufacturer as well as physicians and patients. They offer safe and convenient ways of active pharmaceutical ingredients (API) administration with excellent physicochemical stability in comparison to some other dosage forms, and also provide means of accurate dosing. They can be mass produced with robust quality controls and offer different branding possibilities by means of colored film coating, different shapes, sizes or logos.[3]

Capsules are solid dosage forms in which drug is enclosed within either a hard or soft soluble shell. The shells are generally made up of gelatin. The capsules may be regarded as the container drug delivery system for powder and non powder filling such as tablets, capsules and pellets.[4]

Table: Granulation Methods

Method	Advantage	Limitations
Direct compression	Simple, economical process, No heat or moisture, so good For unstable compounds.	Not suitable for all API, generally limited to lower dose compounds, Segregation potential, expensive excipients
Wet Granulation	Robust process, reduce Elasticity problems, wettablity, reduced segregation potential.	Expensive, Time and energy consuming, Specialized equipment, Stability issues.
Wet Granulation (Non Aqueous)	Vacuum drying technique, Suitable for moisture sensitive API	Expensive equipment, solvent recovery issues, needs organic facility, health and environmental issues.
Dry Granulation	Eliminates exposure to Moisture and drying	Dusty procedure, slow process, not Applicable for all API

Manufacture of capsules [5, 6]

Immediate-release or Altered release hard gelatin capsules require the following common operations.

- Rectification i.e. body-end downward orientation
- Separation of caps from bodies
- Dosing of Fill Material (Powder or Non powder filling)
- Replacement of caps and ejection of filled capsules
- Finishing includes de-dusting and polishing.

Extended Release Formulation [7]

The formulated solid oral dosage form when administered reaches the absorption site and ends with its elimination in the original or modified form, through the normal channel of excretion. Hence in order to prolong the residence of drug in the body, dosing interval can be extended either by

- Altering the release rate of a dosage form to retard the rate of absorption (ka)
- Slowing down of biotransformation rate
- Manipulating the drug molecule to reduce the rate of elimination(kel)

Retarding the absorption rate in designing drug product provides well controlled drug concentration in blood stream. It is also necessary to take into account the physiological constraint of a finite residence time at the absorption site as in case of GI transit time.

Marketed formulations [9-13]

Aceclofenac

Trade name	Strength	Dosage form	Manufacturer
Indian brands			
Valus–A	100mg	Tablet	Glenmark
Aroff	100mg	Film coated tablet	Unichem
Fastanac SR	200mg	Sustained release tablet	Lupin
Aceclo	200mg	Sustained release FC tablet	Aristo
Zerodol CR	200mg	Controlled release tablet	IPCA
Zynac	150mg/ml	Injection	Zydus
International brands			
Preservex	100mg	Film coated tablets	Almiralltd
Airtal	100mg	Tablet	Highnoon
Bristaflam	100mg	Oral powder	Bristoll Mayer Squibb

Misoprostol

Trade name	Strength	Dosage form	Manufacturer
Indian Brands			
Misoprost	Misoprostol25,100,200mcg	Tablet	Cipla
Prestakind	Misoprostol200mcg	Tablet	Mankind
Misolast	Misoprostol200mcg	Tablet	FDC
International brands			
Cytotec	Misoprostol200mcg	Tablet	GDSearleLLC
Cyprostol	Misoprostol200mcg	Tablet	Idis
Gymiso	Misoprostol200mcg	Tablet	HRAPharma
Apo-Misoprostol	Misoprostol100,200mcg	Tablet	Apotex
Misotrol	Misoprostol200mcg	Tablet	Sanofi Aventis

Rationale for extended-release dosage forms [8]

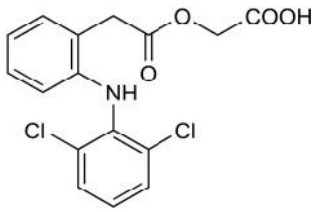
Increase in time interval required between doses. This provides a reduction in the total number of doses required per day. Reduction in fluctuation of drug blood levels about the mean. A controlled release dosage form decrease the drug concentration's fluctuation by, Reducing the blood levels (C max) thus potentially reducing dose related adverse effects.

Drug profile [14-21]

Drug name : Aceclofenac

Chemical name : [[[2-[(2, 6-Dichlorophenyl) amino] phenyl] acetyl] oxy] acetic acid.
Synonym : Aceclofenaco,Aceclofenacum,Aceclofenakas
CAS number : 89796-99-6
Mol.formula : C16H13Cl2NO4
Mol.weight : 354.2
Melting point : 149° to 150° C
Origin of substance : Synthetic

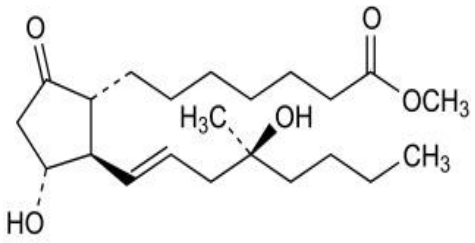
Structure :



Drug name : Misoprostol

Chemical name : (11α, 13E)-11,16-Dihydroxy–16–methyl–9–oxoprost–13–en–1–oic acid methyl ester
Synonym : Misoprostolum, Mizoprostol
CAS number : 59122-46-2
Mol.formula : C22H38O5
Mol.weight : Average: 382.5341 Monoisotopic: 382.271924326
Origin of substance : Synthetic

Structure :



(11*R*, 16*S*)-Form

Conclusion

A Tablet in Capsule device containing Aceclofenac ER tablet and Misoprostol IR tablet for Pain Management with Gastro protection was formulated. Rationale of combining a NSAID and a prostaglandin analogue was well justified and the design of drug delivery system was made simple by encapsulating two different tablets (Aceclofenac and Misoprostol) in single capsule and it offers advantage in terms of GI protection, Patient Compliance and Chrono-therapeutics. Aceclofenac extended release tablet 200mg was formulated using various grades of hydrophilic polymer such as HPMC E50, HPMC K100 LV CR, HPMC K4M CR and HPMC K15M CR as release retardant to prolong the release for 12 hr .Misoprostol Immediate release tablet 200mcg was formulated using Crospovidone as super-disintegrant at 2%, 3% and 4%.Formulation characteristics such as pre-compression and post-compression studies of the developed formulations were carried out separately as per standard procedures. The tablets were found to be within the limits with respect to uniformity of weight, hardness, thickness, diameter, friability and drug content.

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