FORMULATION AND INVITRO EVALUATION OF AZATHIOPRINE COLON TARGETED RELEASE TABLETS

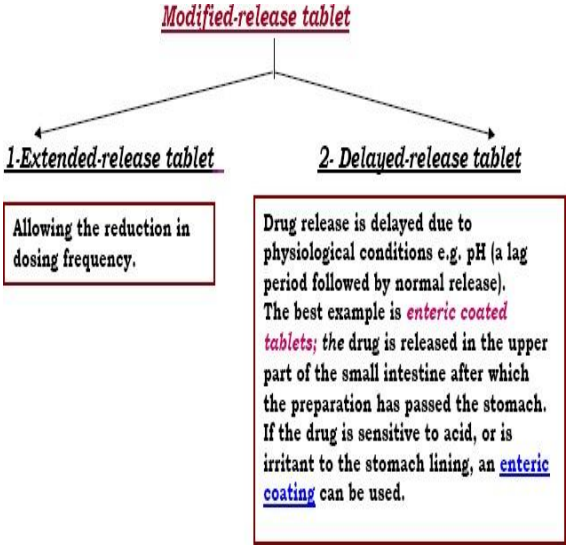
K. CHAITANYA PRASAD
Assistant Professor
Department Of Pharmaceutical Chemistry
Samskruthi College Of Pharmacy
,Hyderabad

Abstract

Drug delivery systems (DDS) are a planned tool for increasing markets/indications, increasing product half life and creating chances. This is only one popular route for systemic effects due to its ease of, pain, ingestion, escaping, versatility and most prominently, patient compliance. Oral delivery products do not require sterility conditions and are therefore, they are not expensive to production.

INTRODUCTION TO COLON

Colon is being extensively investigated as a drug delivery site. CDDS has been growen by means of combination of 1 or more CR mechanisms, hardly releases drug in the upper part of the GIT, but quickly releases drug in the colon following OCDDS .



Delayed Release

A Delayed Release dosage form is designed to release the drug at a time other than promptly after administration. Dosage forms can be designed to modify the release of the drug over a given time or after the dosage form reaches the required location.

Important Reasons for Enteric Coating are as follows:

- To guard acid-liable drugs from the gastric fluid
- To care for gastric distress or nausea due to irritation from drug
- To deliver drugs intended for local action in the intestines
- To deliver drug that are optimally absorbed in the small intestine to their primary absorption site in their most concentrated form
- To provide a delayed release component to repeat actions
- Protect the drugs from harmful effect of the gastric contents, some of the drugs are prone to be hydrolyzed in acid media (For example Pantoprazole)

Enteric Coating Materials:

1. Cellulose Acetate

2. Polymethacrylic Acid/Acrylic Acid Copolymer
3. Hydroxy Propyl Methyl Cellulose Phthalate
4. Polyvinyl Acetate Phthalate
5. Hydroxy Methyl Ethyl Cellulose Phthalate
6. Acrylic Resin and Shellac

COATING TECHNOLOGIES

In the pharmaceutical industry, significant advances have been achieved in polymer coating of solid dosage forms over the last two decades. Polymer coating involves deposition of a uniform membrane of polymer onto the surface of the substrates, such as tablets, spheres or pellets and drug particles. Coating techniques that are used in developing controlled release reservoir or osmotic systems include

(a) Film Coating

(b) Layering Coating

(c) Compression Coating

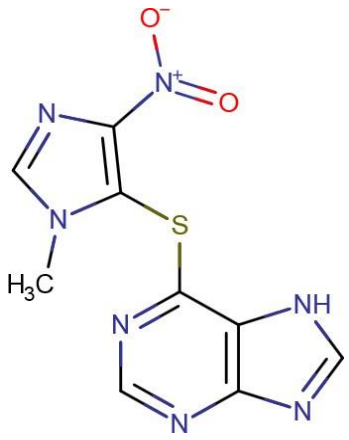
- Final Formulation Development Based On The Pre And Post Compression Results.

To perform preformulation parameters like:

- Constriction of standard linearity curve of Azathioprine.
- Drug-excipients compatibility study by FT- IR spectrophotometer.
- Bulk density and tapped density
- Angle of repose
- Compressibility index and hausner's ratio

DRUG PROFILE

DRUG NAME: Azathioprine



Synonyms:

- 6-((1-Methyl-4-nitro-1H-imidazol-5-yl)thio)-1H-purine
- 6-(1'-Methyl-4'-nitro-5'-imidazolyl)-mercaptopurine
- Imuran (tn)

Weight:Average: 277.263

Chemical Formula: C9H7N7O2S

IUPAC Name: 6-[(1-methyl-4-nitro-1H-imidazol-5-yl)sulfanyl]-7H-purine

EXCIPIENT PROFILE SSG

Nonproprietary Name: Sodium Starch Glycolate

Synonyms: Carboxymethyl starch, sodium salt; Primojel; Tablo

Chemical Name: Sodium carboxymethyl starch

Chemical Name: Sodium carboxymethyl starch

Structural Formula

MICROCRYSTALLINE CELLULOSE:

Nonproprietary Names:

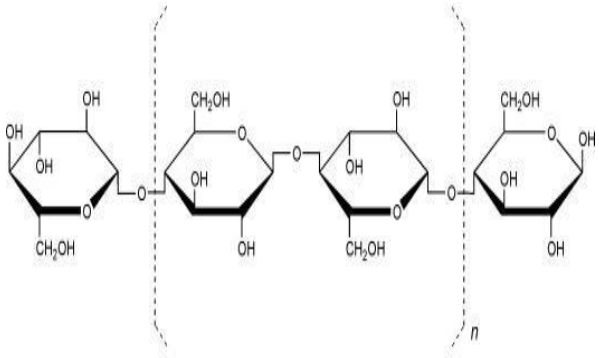
- BP: Microcrystalline cellulose
- USPNF: Microcrystalline cellulose

Synonyms:

PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.

Functional Category:

Adsorbent, suspending agent, tablet and capsule diluent and tablet disintegrant.



Materials and methods

Materials	**suppliers**
Azathioprine	Chandra labs, Hyderabad
Microcrystalline cellulose	Mylon Chemical Reagents
Cross povidone	Mylon Chemical Reagents
Cross caramellose sodium	Standard Chemical Reagents
Sodium starch glycolate	Standard Chemical
	Reagents
Magnesium stearate	Standard Chemical Reagents
Lactose monohydrate	Mylon Chemical Reagents
Talc	Mylon Chemical Reagents

EQUIPMENTS

Table no: List of equipments

Equipments	**Model /Company**
Electronicbalance	Citizen,India
Tabletcompressionmachine	Cadmachsinglepunchmachine
Hardness tester	Monsantohardnesstester
Dissolution test apparatus	Lab India
Disintegration test apparatus	CampbellElectronics
Friability test apparatus	RicheRich
U.V visible spectrophotometer	Shimadzu UV-1601,Japan
Fourier transformer infrared spectrophotometer	Bruker(Tensor27)
Hot air oven	Lab india

METHODOLOGY:

PREFORMULATION STUDIES

Preformulation studies are performed to investigate the physical and chemical properties of a drug substance alone and also when combined with other substances such as excipients. It is the first step in the rational development of dosage forms.

Flow Properties

- Angle of Repose
- Bulk density
- Tapped density
- Compressibility index and Hausner ratio

Drug – Excipient Compatibility Study:

FTIR spectrum is useful to identify functional group interaction between the API and excipients.

Evaluation of rapid releasecore (RRCT) and press-coated tablets Of Azathioprine EVALUATION OF TABLETS:

- Physical Appearance
- Size & Shape
- Weight variation test
- Content Uniformity
- Thickness and diameter
- Hardness
- Friability

RESULTS

DRUG EXCIPIENT COMPATIBILITY STUDIES:

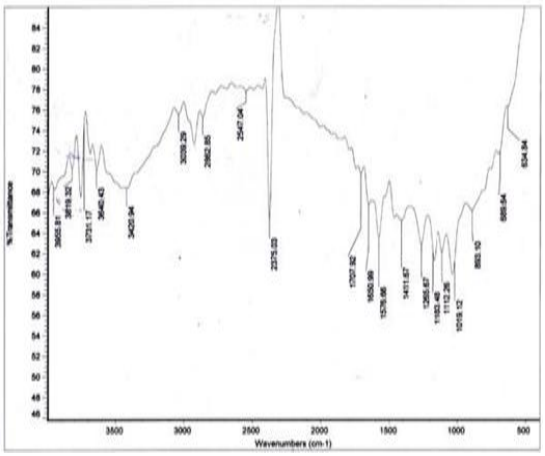


Figure - FTIR Spectra of Azathioprine pure drug

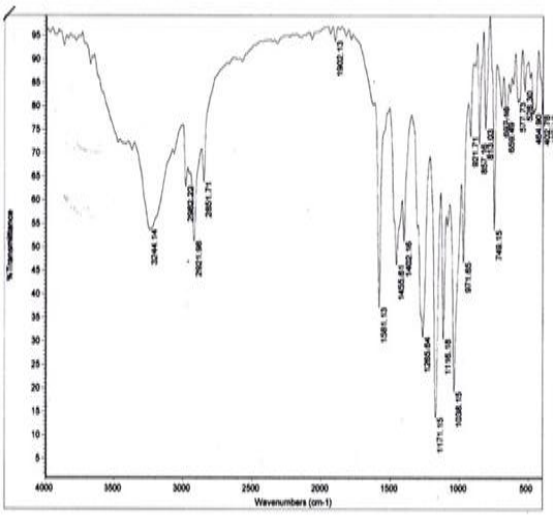


Figure - FTIR Spectra of Azathioprine optimized formulation

PRE COMPRESSION PARAMAETRS

Precompression parameters

Formulations	Angle of Repose (θ)	LooseBulk Density (g/ml)	Tapped Bulk Density (g/ml)	%Compressibility	Hausner'sratio
A1	20°52'	0.507	0.580	13.57	1.12
A2	21°42'	0.411	0.486	12.71	1.14
A3	24°02'	0.420	0.492	11.59	1.16
A4	25°16'	0.306	0.350	12.56	1.12
A5	24°84'	0.308	0.347	14.85	1.14
A6	26°56'	0.322	0.379	13.48	1.15
A7	24°96'	0.404	0.470	12.42	1.16
A8	25°41'	0.515	0.572	12.39	1.14
A9	24°60'	0.508	0.571	13.37	1.12

POST COMPRESSION PARAMETERS

Tooling:

8mm round shape for core tablet

12mm round shape tooling for press coat.

Evaluation of rapid release core (RRCT) and press-coated tablets of Azathioprine Tablet compression parameters:

Weight of the tablet 150 mg(core tablet) 450mg(press coated tablet)

Hardness range 5.2Kg/cm2 (core tablet)

6.0 Kg/cm2(press coat tablet)

Thickness range 3.2 ± 0.2 mm (core tablet) 3.4± 0.1mm(press coat tablet)

Evaluation for rapid release core

Physical parameter	A1	A2	A3	A4	A5	A6	A7	A8	A9
Avg Weight (mg)	150	151	149	148	151	150	149	150	149
Hardness (Kg/cm²)	5.1	5.3	5.4	5.2	5.1	5.4	5.3	5.7	5.5
Thickness (mm)	3.47	3.49	3.5	3.51	3.50	3.48	3.46	3.6	3.5
Friability %	0.31	0.41	0.45	0.53	0.50	0.42	0.39	0.40	0.38
Disintegration time	3min42sec	3min38sec	3min4sec	3min18sec	2min14sec	2min06sec	4min14sec	3min28sec	3min20sec

Buffer Stage:

Medium : 6.8pH phosphate buffer

Type of apparatus : USP - II (paddle type)

RPM 50

Volume : 900ml

In vitro dissolution for core tablets were done in 0.1N HCL and enteric press coated tablets were initially placed in acidic stage and next was changed with phosphate buffer.

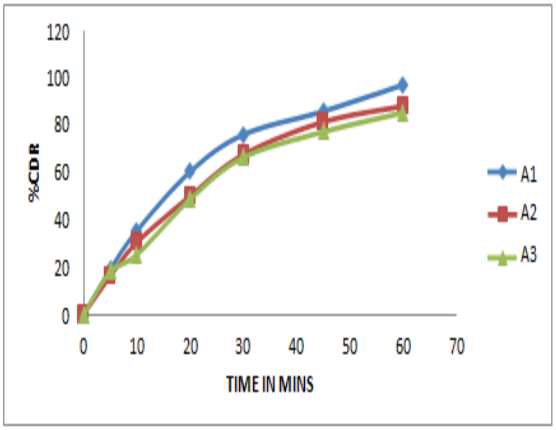


Figure - Dissolution graph for formulations A1-A3

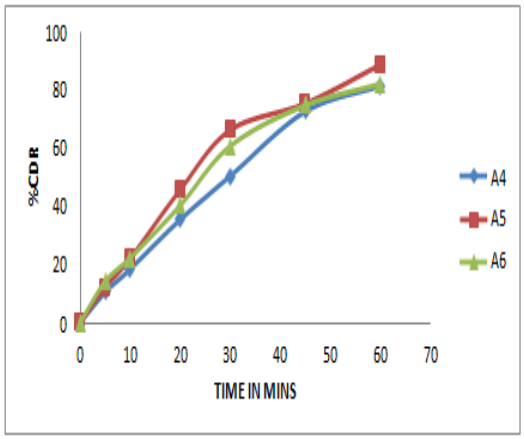


Figure: Dissolution graph for formulations A4-A6

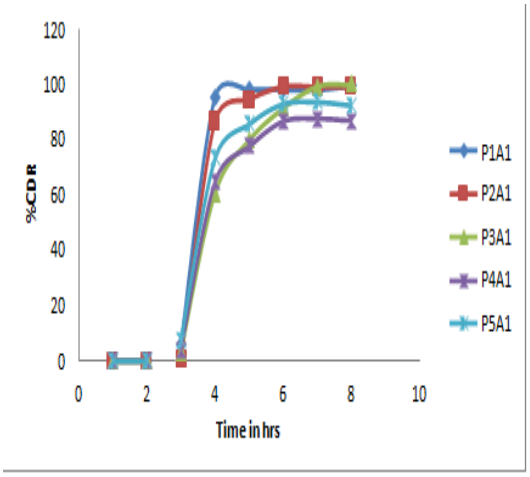


Figure - Graph showing % CDR verses time in hrs for formulations P1A1 to P5A1

CONCLUSION

The following conclusions were drawn from the study:

- CDDS was designed by direct compression to develop quick release of core preparation. It exhibits their action straightly on colon.
- The pre-formulation of all preparations showed good flow properties and these can be used for tablet manufacture.
- The post-compression parameters of all preparations were estimated and the values were found to be acceptable.
- From the in-vitro dissolution profile of the quick release core preparations, it was fulfilled that the A1preparation i.e. the formulation containing CP, MCC and 2% of Mg. stearate is the better development.
- For the above A1 rapid release core development press coat was done by using 175mg HPMC 175mg EC.
- So finally based on all Parameters P3F1 was optimized formulation.

SUMMARY

The major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor aqueous solubility.

Azathioprine, An immunosuppressive antimetabolite pro-drug.It is used in the treatment of rheumatoid arthritis. The tablets were designed using polymers EC and HMPC. The main aim was to optimize the formulation for 8 hrs in-vitro release with the use of polymers. Optimized formulation containing HPMC and EC polymers in order to delay the release and show exactly release of drug at targeted site with longer action.

REFERENCES

1. Sarasija S and Hota A. Colon-specific drug delivery systems. Ind. J. Pharm. Sci. (2000) 62: 1-8.

2.http://www.ncbi.nlm.nih.gov/pubmed/20848388

3. Sinha, V. R., Mittal, B. R., Bhutani K. K., Rachna Kumari, Colonic drug delivery of 5-fluorouracil: an in vitro evaluation. Int. J Pharm, 269: 101-108, 2004.

4. E C Van Os, B J Zins, W J Sandborn, D C Mays, W J Tremaine, D W Mahoney, A R

Zinsmeister, and J J LipskyAzathioprine

El-Malah Y1, Nazzal S. Preparation of delayed release tablet dosage forms by compression coating: effect of coating materia