



CODEN [USA]: IAJ PBB

ISSN : 2349-7750

**INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES**

SJIF Impact Factor: 7.187

<http://doi.org/10.5281/zenodo.4705305>Online at: www.iajps.com

Research Article

**DESIGN AND DEVELOPMENT OF CORE IN-CUP TABLET OF
AZATHIOPRINE**Swalin Parija¹, Guru Prasad Mohanta², Upendra Nath Nanda³¹Institute of Pharmacy & Technology, Salipur, Cuttack, Odisha-754202.²Annamalai University, Annamalai Nagar - 608002³Seemanta Institute of Pharmaceutical Sciences, Jharpokharia, Mayurbhanj, Odisha- 757086

Article Received: March 2021

Accepted: March 2021

Published: April 2021

Abstract:

Colon targeted drug delivery has gained increasing significance for the delivery of drugs for the treatment of local diseases. To accomplish a successful colonic delivery a drug desires to be protected from absorption in the GI tract and immediately release in to the proximal colon which is considered the optimum site for colon-targeted delivery of drugs. The purpose of this study is to explore the possibility of core in cup tablet as a novel carrier for colonic delivery of a sparingly soluble drug, Azathioprine. The study involves designing a tablet for colon-target which consists of a central blended form of drug and polymer core and were further coated with different concentrations of CAP to thin film and fine thickness and finally the core-in-cup is over coated with pH-sensitive polymer, by spray coat method to provide acid and intestinal resistance. In vitro drug release studies of tablets were carried out in different dissolution media, i.e., 0.1 N HCl (pH 1.2), phosphate buffers pH 6.8 and 7.4, The physicochemical parameters of all the formulations were found to be in compliance with the pharmacopoeial standards. The stability studies of all formulations were performed as per ICH guidelines. The results demonstrated that the tablets coated with cellulose acetate phthalate 5%, 7.5 % and 10% w/w showed a sustained release of 98.60% for 24 h in the colon. Drug release study in simulated pH7.4 phosphate buffer (colonic fluid) revealed the delayed release nature of Eudragit coating. Kinetic data proved that the optimized colon drug delivery system was fitted well into zero-order kinetics, and apparent lag time was found to be 5 hours, followed by peppas release model.

Keywords: Azathioprine, Biodegradable gums, Eudragit, film coat, core in cup tablet**Corresponding author:****Swalin Parija,**

Asst. Professor,

Institute of Pharmacy & Technology,

Salipur, Cuttack, Odisha-754202

Ph-9439484995

Swalinpharma@Gmail.Com

QR code



Please cite this article in press Wafaa Altaezi et al., *Design And Development Of Core In-Cup Tablet Of Azathioprine.*, Indo Am. J. P. Sci, 2021; 08(04).

INTRODUCTION:

Mainly the colon specific drug delivery system has provided the importance for drugs, which are especially absorbed from colon region by preventing the degradation in upper gastrointestinal tract (GIT). Drug release at this site will ensure maximum therapeutic benefits[1] Colon-targeted delivery systems are convenient for treating localized colonic diseases, i.e., Crohn's disease, ulcerative colitis, and constipation, which can be treated most efficiently by local delivery of drugs.[2] The colon-specific delivery system should protect the drug from absorption in the stomach and small intestine, thus prevent a sudden onset of drug release upon entry into less aggressive ambience of the colon. Various drug delivery approaches have been developed for colon-specific drug delivery, which include pH-sensitive system, time-dependent system, pro-drugs, and microflora-activated system to deliver anti-inflammatory agents to the sites of inflammation, and hence systemic drug absorption should be reduced as this leads to unwanted systemic side effects [3]. Of all the systems formulated for colon-specific drug delivery, pH-sensitive system and time-dependent system are mostly used.[4] The pH variation along the GIT is based on the strategy of using pH as a trigger to achieve drug release in the colon. The high individual variability together with similarity in pH between the small intestine and the colon make the site specificity of pH-dependent system not very reliable[5]. Most of the strategies in time-dependent drug delivery are dependent on the principle to delay the drug release until approximate influx in the colon region. Although the relative consistency of transit times in the small intestine is because of the potentially large variation in gastric emptying time, the colon influx time cannot be exactly predicted. Therefore, by suppressing drug release in the stomach and thus reducing the effect of variations in gastric residence time, appropriate integration of pH-sensitive and time-dependent systems in a single dosage form should improve colon drug delivery. The release of water-soluble drug from a water-soluble polymeric platform is often rapid, and therefore hydrophobic polymer may be included within the matrix formulation to offer a greater control drug release [6]. Core-in-cup tablets have been developed by direct compression based on combination of hydrophobic polymers and a gelling hydrophilic polymer, microcrystalline cellulose, to achieve a 20-h sustained release formulation of Azathioprine tablets using Cellulose acetate phthalate as coating polymer to produce a delivery system in which the release of drug is modulated. Cellulose acetate phthalate coat was employed to delay the penetration of dissolution medium into the matrix,

thereby decreasing drug release rate [7]. Azathioprine an immunosuppressive antimetabolite, Azathioprine is a prodrug of 6- mercaptopurine that is further metabolized by various enzymes present in the liver and gut have proven efficacy in the treatment of inflammatory bowel disease. Its parent drug 6-mercaptopurine (6-MP), and the closely related 6-thioguanine (6-TG), were originally developed for their anticancer properties, but thiopurines as a class are now more widely used for their anti-inflammatory and immunosuppressant effects. Azathioprine and 6-mercaptopurine may be effective for inducing remission in Crohns disease among patients with chronically active disease. These drugs may reduce the need for steroid treatment and their use may therefore lead to a lower incidence of steroid related side effects The bioavailability of this drug upon oral ingestion is limited to an extent of 41-50%. It has low biological half life of 3-5 hours. To overcome these drawbacks, the present study was undertaken to investigate the colon targeted drug delivery system of Azathioprine through core and cup technique. Due to the distal location of the colon in the gastrointestinal tract, core and cup technique should prevent drug release in the stomach and small intestine and produce an gradual onset of drug release upon entry into the colon [8].

MATERIALS AND METHODS:

Azathioprine was generously gifted by RPG Life Sciences Ltd. (Mumbai, India). All the chemicals utilized were of suitable analytical grade and used as and when required. Biodegradable-natural Gums were procured from Nutriroma Company at Hyderabad and all the chemicals required were purchased from national scientifics, Guntur.

Preparation of Azathioprine core tablet:

The controlled release matrix tablet of Azathioprine was prepared by wet granulation method [9]. The required quantities of Azathioprine, PVPK-30 (as a binder), Moringa olifera gum or Okra gum (as a polymers) and lactose (as a diluent) were weighed as per formula given in Table 1 and these ingredients were mixed uniformly and prepared a wet mass by addition of binder solution. The wet mass was passed through sieve number #12 and allowed to drying for 30 minutes in a tray dryer for 600C. The dried granules were passed through the sieve number #16 and finally lubricated with talc and magnesium stearate. The obtained dry granules were weighed into individual tablets and finally compressed into the tablet by 16 station rotary tablet compression machine using 9mm flat punches. (RIMEK, Karnavati Engineering Ltd., Gujarat, India).. The core tablets of AZA having an average weight of 300

± 5 mg were prepared by direct compression. Different gums were used as binders cum hydrophilic matrix former, anhydrous lactose as diluents and magnesium stearate as lubricant, Talc as glidant [10]. Fifty core tablets and compression-coated tablets were prepared in duplicate Preparation of cup tablet: The cup formulations were formulated by direct compression technique. In which the required

quantities of Eudragit RS100 and microcrystalline cellulose according to the formula shown in Table- 2, were weighed and mixed uniformly and finally the powder mixture was compressed by 16 station rotary tablet compression machine by using special punch designed and fabricated, to prepare cup tablets. The newly designed upper 12 mm punch has protrusion and lower punch (12mm) remains flat faced [11].

Table 1: Azathioprine Core formulations:

Ingredients	F1	F ₂	F ₃	F ₄	F ₅	F ₆
Azathioprine	50	50	50	50	50	50
Povidone	10	10	10	10	10	10
Moringa olifera gum	25	50	75	-	-	-
Okra gum	-	-	-	25	50	75
Lactose	111	86	61	111	86	61
Magnesium stearate	2	2	2	2	2	2
Talc	2	2	2	2	2	2
Total	200	200	200	200	200	200

Evaluation of granules:

Flow properties of the prepared granules were evaluated. Other properties of the granules evaluated were bulk density, true density apparent density, and porosity using standard reported methods⁶. weight variation test was conducted as per specifications of IP. Hardness and friability of the tablets formulated were evaluated using a Monsanto hardness tester and a Roche friabilator, respectively. [12]

Preparation of core in cup tablet:

The cups were placed in a 12mm die cavity and core tablet was inserted into the cups and compressed with 12mm flat faced punches. The composition of the core in cup tablets was given in Table 3.

Enteric coating:

Core in cup tablet were further coated with enteric coating polymer (cellulose acetate phthalate) by spray coating method. 9% cellulose acetate phthalate in 8:2 (v/v) mixture of acetone: ethanol plasticized with dibutylphthalate (0.75%), was used as a coating solution. Talc (0.1% w/v) was added as antiadherent and the solution was stirred for 15 min. Placed the core in cup tablets into a coating pan, the coating solution was sprayed over the tablets by R&D coater, rotating with a speed of 15 rpm, the pressure of the spray gun was maintained at 0.1 M.Pa and the air temperature was maintained at 35-40°C. The tablets were coated to a 5%, 7.5 % and 10% w/ w total weight gain. [13]

Post compression evaluation of Azathioprine tablets [14]:

Weight variation: For estimating weight variation, 20 tablets of each formulation were weighed using an electronic balance (Denver Instrument, Gottingen, Germany) and the test was performed according to the official test.

Thickness: The thickness of the tablet was measured using a Digital Vernier Calliper (Mitutoyo Digimatic Calliper, Kanagawa Japan).

Hardness: The crushing strength of ten tablets was measured using Monsanto tablet hardness tester (Interlabs, Ambala, India). A tablet hardness of about 5-7 kg/cm is considered adequate for mechanical stability.

Friability: The friability of the tablets was determined in Roche Friabilator (Model 902, EI product, Panchkula, India). Ten tablets were weighed accurately from each batch of tablets and placed in the tumbling chamber and rotated at 25 rpm for a period of 4 min. Tablets were taken and again weighed. The percentage loss was determined by using the formula % **Friability = $\frac{\text{Initial weight of tablets} - \text{Final weight of tablets}}{\text{Initial weight of tablets}} \times 100$** The results of Post compression parameters were reported in **Table-5**

Estimation of drug content: The drug content in each formulation was determined by triturating 20 tablets and The drug equivalent to 50 mg was placed in 100 ml volumetric flask and final volume was made up to 100 ml with 6.8 pH phosphate buffer. Then the samples were taken with suitable dilutions and concentration of drug in the samples was measured by using U.V visible spectroscopy at 285 nm. [15]

Determination of post Compressional parameters of cup tablets [16]:

Depth of the cavity: Depth of the cavity of cup tablets was determined by using thread and scale.

Friability: The friability test for cup tablets were determined by using Friabilator .

Thickness: The thickness of the cup tablets were determined by using Vernier calipers .

Evaluation studies of enteric coated Azathioprine core in cup tablets:

Disintegration test for enteric coated Azathioprine core in cup tablets: Compendial in-vitro test methods for enteric coated tablets have traditionally relied on a two stage disintegration type test in order to confirm enteric performance. Six tablets were initially treated in tablet disintegration tester using 0.1 M HCl for 2 hrs, then the tablets were subjected to further 3 hr in 7.4 Phosphate buffer[17].

Dissolution test for enteric coated Azathioprine core in cup tablets:

In-vitro dissolution studies of enteric coated core in cup tablets were possessed by using dissolution apparatus (USP II) paddle method. Enteric coated core in cup tablet formulations were selected based on dissolution studies for the core tablets. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were sequentially used referred to as sequential pH change method. When performing experiments, the pH 1.2 medium was first used for 2 hours (since the average gastric emptying time is 2 hrs.), then removed and the fresh pH 7.4 phosphate buffer saline (PBS) was added. After 3 hours (average small intestinal transit time is 3 hrs.), then the medium was removed and colonic fluid pH 6.8 buffer was added for subsequent hours. Nine hundred milliliters of the dissolution medium were used at each time. Rotation speed was 100 rpm and temperature was maintained at $37 \pm 0.5^\circ\text{C}$. Enteric coated Azathioprine core in cup tablets equivalent to 50mg of Azathioprine was used in each test. Five milliliters of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were at 281 nm for Azathioprine respectively, by UV absorption spectroscopy and the cumulative percentage release was calculated over the sampling times[18].

RESULTS AND DISCUSSION:

In the present investigation-controlled release formulations of core tablets for per-oral administration using natural gums in order to increase its biological half and to determine the influence of formulation and preparation variables on matrix

tablets characteristics. The granules were characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio. The parameters for evaluation of granules are depicted in Table 4. The angle of repose of different formulation batches from F1 to F6 was found to be from $24.02^\circ \pm 0.21^\circ$ to $29.31^\circ \pm 0.18^\circ$. The angle of repose was less than 30° for all the formulation batches of granules, indicating good flow behavior. Similarly, bulk density and tap density of all the formulation batches from F1 to F6 were found to be from 0.429 ± 0.021 to $0.478 \pm 0.014\text{g/ml}$ and from 0.507 ± 0.025 to $0.580 \pm 0.021\text{g/ml}$, depicting good flow properties of the granules. The Carr's index of all formulation batches was in the acceptable range from 13.94 ± 0.43 to 14.93 ± 0.46 . The Hausner ratio of all formulation batches from F1 to F6 was found to be from 1.16 ± 0.09 to 1.21 ± 0.011 . The Hausner ratio less than 1.25 indicates good flowability.

The weight of each tablet was determined to be within the range of 200 ± 5 mg in order to maintain the relatively constant volume and surface area. All the formulated preparations were subjected to weight variation, hardness, friability and drug content. All tablets complied I. P. weight variation test requirement. The hardness was found to be in between 4 - 5 kg. The tablets satisfied USP friability requirement, as the % friability values are less than 1%. The percent drug content was found to be with in 98 - 102% of the labeled amount and hence complied drug content requirement. The core tablet was successfully coated by coating technique and further core-in-cup tablet was coated with varying proportion of Cellulose acetate phthalate. The results of the *in vitro* dissolution studies of different batches of coated tablets indicated that increase in concentration of Cellulose acetate phthalate from 5% to 7.5% w/w and 10% w/w and keeping constant weight gain in thickness of polymers at 10% w/w, the lag time (the time required for drug release in SCF) was significantly increased to 5h. The lag time was determined by separately running dissolution studies of Cellulose acetate phthalate coated (5% to 7.5% w/w and 10% w/w) tablets in SCF for 5 hours at minimum time intervals. The amount of Cellulose acetate phthalate coat was the key factor for such lag time. Lower amount of Cellulose acetate phthalate coat shows shorter lag time, and higher amount shows longer lag time. Core-in-cup tablet with a coating level of 10% w/w showed a lag time of 5 hr corresponds to time required to reach colonic region.

During dissolution studies, it was observed that, the enteric coated core in Cup tablets was intact for 2 hrs in pH 1.2, and also in intestinal pH 7.4. With all the

formulations, there was absolutely no drug release in pH 1.2 and also in intestinal pH 7.4., thus indicating the efficiency of 9% CAP for enteric coating.

From the *In-vitro* release studies of Core-in-cup tablet, it was observed that with all formulation, there was absolutely no drug release in simulated gastric fluid (acidic pH 1.2) for 2 hours and in simulated intestinal fluid (pH 7.4 phosphate buffer). But slow release was found in colonic medium (pH 6.8 phosphate buffer). *In-vitro* release profiles in colonic medium were found to have very good sustaining efficacy and shown in figure 1&2. The tablets prepared with Moringa olifera gum in 1:0.5, 1:1 and 1:1.5 ratios shown sustained drug release for a period of 10 hours, 11 hours and 12 hours respectively and tablets prepared with gum karaya in 1:0.5, 1:1 and 1:1.5 ratios shown sustained drug release for a period of 9 hours, 10 hours and 11 hours respectively.

To ascertain the mechanism of drug release, the dissolution data was analyzed by zero order, first order, and Higuchi and peppas equations. When the amount of drug release values was plotted against time straight lines were obtained in all the cases indicating that the rate of drug release from these matrix tablets followed zero order kinetics. The plot of log % Drug Released vs log time (peppas plots) were drawn. The plots were found to be linear with all matrix tablets. Release Kinetics of matrix tablets, the time required to get 50% drug release (T_{50}) and 90% drug release (T_{90}) was calculated and were shown in Table 8. The exponential coefficient (n) values were found to be in between 0.7385 to 0.8732, indicating that the drug release followed non fickian mechanism. These results indicated that the release rate was found to decrease with increase in concentration of natural polymer employed.

Table 2: Azathioprine Cup formulations

Ingredients	C ₁	C ₂	C ₃	C ₄	C ₅	C ₆
Eudragit RS100	400	400	400	400	400	400
MCC	42	42	42	42	42	42
Mg. stearate	4	4	4	4	4	4
Talc	4	4	4	4	4	4
Total	450	450	450	450	450	450

Table 3: Azathioprine Core in cup formulations:

S.No	Core in cup formulations	Combination of core and cup formulations
1	ACC ₁	F ₁ (core) + C ₁ (cup)
2	ACC ₂	F ₁ (core) + C ₂ (cup)
3	ACC ₃	F ₁ (core) + C ₃ (cup)
4	ACC ₄	F ₁ (core) + C ₄ (cup)
5	ACC ₅	F ₁ (core) + C ₅ (cup)
6	ACC ₆	F ₁ (core) + C ₆ (cup)

Table 4: Micromeritic properties of formulation blend of Azathioprine core tablets

Formulation	Evaluation parameters				
	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's Ratio	Angle of Repose (θ)
F ₁	0.429 ± 0.021	0.507 ± 0.025	14.93 ± 0.46	1.18 ± 0.019	28.96 ± 0.17
F ₂	0.442 ± 0.023	0.511 ± 0.031	14.24 ± 0.51	1.18 ± 0.013	29.02 ± 0.18
F ₃	0.477 ± 0.019	0.571 ± 0.021	14.67 ± 0.44	1.16 ± 0.09	29.31 ± 0.18
F ₄	0.439 ± 0.012	0.512 ± 0.022	14.24 ± 0.32	1.16 ± 0.012	24.02 ± 0.21
F ₅	0.445 ± 0.009	0.522 ± 0.012	13.94 ± 0.43	1.17 ± 0.09	25.22 ± 0.13
F ₆	0.478 ± 0.014	0.580 ± 0.021	14.58 ± 0.25	1.21 ± 0.011	27.36 ± 0.12

Table 5 : Physical properties of Azathioprine core tablets

Formulation	Parameters				Thickness (mm)
	Weight variation (mg)	Hardness (kg/cm ²)	Friability (%)	Drug content (%)	
F ₁	200 ± 1.7	4.1 ± 0.02	0.23	99.11	2.94±0.04
F ₂	200± 1.9	4.5 ±0.03	0.33	99.34	2.96±0.03
F ₃	200± 2.2	4.2 ± 0.04	0.44	99.26	2.99±0.02
F ₄	200 ± 1.3	4.3 ± 0.03	0.36	99.54	2.96±0.02
F ₅	200 ± 1.5	4.0 ± 0.02	0.49	99.36	2.97±0.03
F ₆	200 ± 1.8	4.2 ± 0.04	0.57	99.43	2.99±0.02

Table 6: Results of post-compressional parameters for cup tablets

S.No	Post-compressional parameters	C ₁	C ₂	C ₃	C ₄	C ₅	C ₆
1	Depth of the cavity (mm)	3.1±0.09	3.1±0.12	3.1±0.07	3.1±0.04	3.1±0.11	3.1±0.07
2	Friability (%)	0.52	0.41	0.37	0.57	0.64	0.63
3	Thickness (mm)	4.53	4.78	4.72	4.76	4.64	4.68

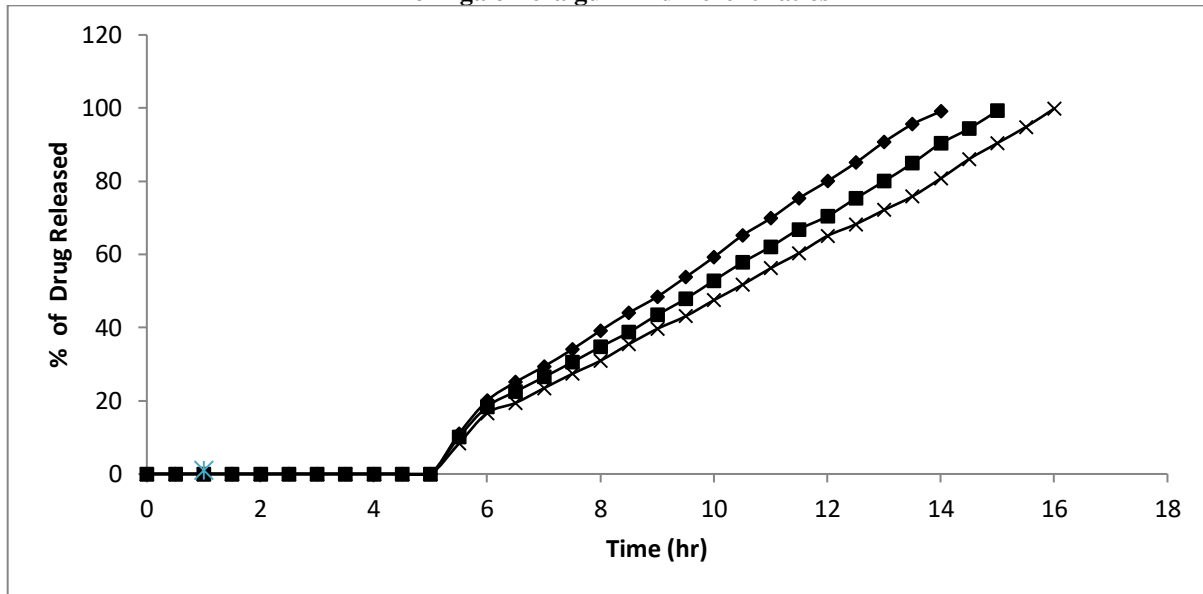
Table 7: Results of Disintegration Test For Enteric coated core in Cup tablets

S.No	Disintegration signs	ACC ₁	ACC ₂	ACC ₃	ACC ₄	ACC ₅	ACC ₆
1	1 st hour	No sign	No sign	No sign	No sign	No sign	No sign
2	2 nd hour	No sign	No sign	No sign	No sign	No sign	No sign
3	3 rd hour	No sign	No sign	No sign	No sign	No sign	No sign
4	4 th hour	No sign	No sign	No sign	No sign	No sign	No sign
5	5 th hour	No sign	No sign	No sign	No sign	No sign	No sign

Table 8: *In vitro* drug release kinetic data of Azathioprine core in cup tablets prepared with Gum kondagogu in different ratios

Formulation	Correlation Coefficient Value				Release Rate Constant (mg/hr)k ₀	Exponential Coefficient (n)	T ₅₀ (hr)	T ₉₀ (hr)
	Zero Order	First Order	Matrix	Peppas				
ACC ₁	0.9991	0.6859	0.9271	0.9968	4.99	0.8732	5.0	9.0
ACC ₂	0.9984	0.8085	0.9352	0.9983	4.40	0.8651	5.6	10.2
ACC ₃	0.9965	0.7450	0.9355	0.9989	4.20	0.8594	5.9	10.7
ACC ₄	0.9907	0.8211	0.9561	0.9956	6.41	0.7385	3.9	7.0
ACC ₅	0.9895	0.8206	0.9573	0.9971	5.81	0.7508	4.3	7.7
ACC ₆	0.9925	0.8353	0.9506	0.9964	5.07	0.7643	4.93	8.88

Figure: 1. Comparative *In-vitro* drug release profile plot of core in cup tablets of Azathioprine prepared with *Moringa olifera* gum in different ratios

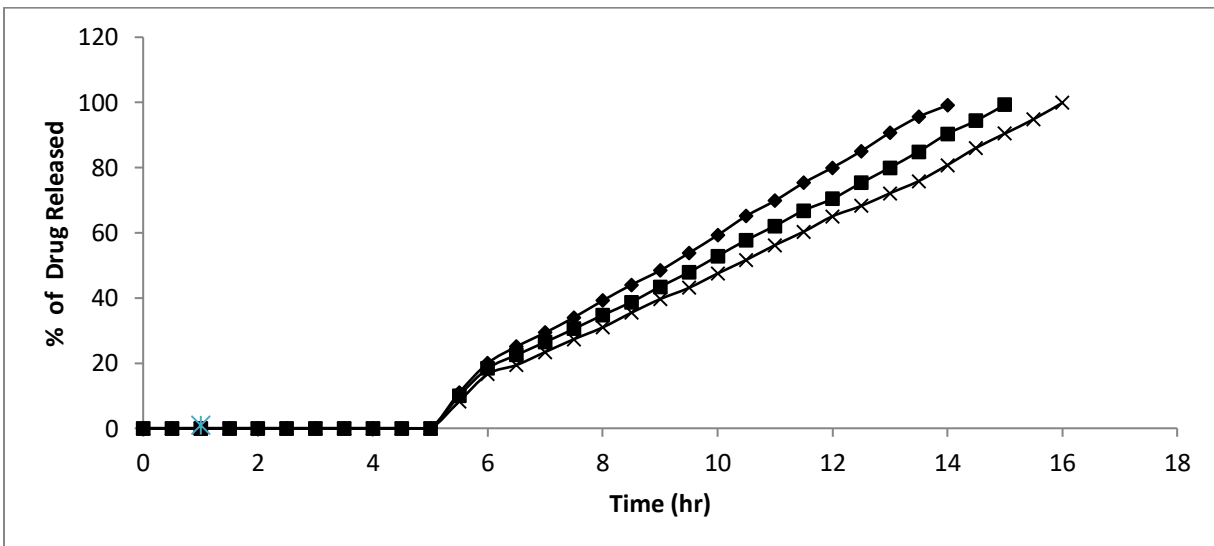


(-■-)ACC1: Formulation prepared with 1:0.5 ratio of drug and polymer.

(-◆-)ACC2: Formulation prepared with 1:1 ratio of drug and polymer.

(-×-)ACC3: Formulation prepared with 1:1.5 ratio of drug and polymer.

Figure: 2. Comparative *In-vitro* drug release profile plot of core in cup tablets of Azathioprine prepared with Okra gum in different ratios



(-■-)ACC4: Formulation prepared with 1:0.5ratio of drug and polymer.

(-◆-)ACC5: Formulation prepared with 1:1 ratio of drug and polymer.

(-×-)ACC6: Formulation prepared with 1:1.5 ratio of drug and polymer.

CONCLUSION:

It is concluded from the present study that appropriate combination of a pH-dependent polymer (Eudragit RS100) with a overcoat of Cellulose acetate phthalate was suitable for adequately

sustained drug release and to protect Azathioprine from being released in the upper region of the GI system. The in vitro drug release studies indicate that the optimized formulation was a promising system targeting Azathioprine to the colon. The drug release

pattern from all formulations was best fitted Korsmeyer-Peppas equation with non-Fickian diffusion kinetics. Tablet with a coating level of 10 % w/w showed a lag time of 5 hr corresponds to time required to reach colonic region. The coating polymers exhibited good results in targeting the colonic study. Formulations F3 was found to be more efficient controlled release in delivering the drug azathioprine to the colonic site analyzed with respect to dissolution release studies. The obtained results showed the capability of the system in delaying drug release for a programmable period of time and the possibility of exploiting such delay to attain colon targeting.

REFERENCES:

- Mundargi RC, Patil SA, Agnihotri SA, Aminabhavi TM. Development of polysaccharide-based colon targeted drug delivery systems for the treatment of amoebiasis. *Drug Dev Ind Pharm.* 2007; 33:255–64.
- Amrutkar JR, Gattani SG. Chitosan-chondroitin sulfate-based matrix tablets for colon specific delivery of indomethacin. *AAPS Pharm Sci Tech.* 2009; 10:670–7.
- Marucci M, Ragnarsson G, Nyman U, Axelsson A. Mechanistic model for drug release during the lag phase from pellets coated with a semi-permeable membrane. *J control Release.* 2008 ;127(1):31-40.
- Mura P, Maestrelli F, Cirri M, González Rodríguez ML, Rabasco Alvarez AM. Development of entericcoated pectin-based matrix tablets for colonic delivery of theophylline. *J Drug Target.* 2003;11:365–71.
- Asghar LF, Azeemuddin M, Jain V, Chandran S. Design and *in vitro* evaluation of formulations with Ph and transit time controlled sigmoidal release profile for colon-specific delivery. *Drug Deliv.* 2009;16:205–13.
- Qi M, Wang P, Wu D. A novel pH- and time-dependent system for colonic drug delivery. *Drug Dev Ind Pharm.* 2003;29:661–7.
- Yang L, Chu JS, Fix JA. Colon-specific drug delivery: new approaches and *in vitro/in vivo* evaluation. *Int J Pharm.* 2002;235:1–15.
- Kotagale N, Maniyar M, Somvanshi S, Umekar M, Patel CJ. Eudragit-S, Eudragit-L and cellulose acetate phthalate coated polysaccharide tablets for colonic targeted delivery of azathioprine. *Pharmaceutical development and technology.* 2010;15(4):431-7.
- Bhavani D, Vijaya Vani CH.S, Uma Maheshwar Rao V. Formulation and evaluation of montelukast sodium pulsatile drug delivery system by core in cup method. *International Journal of Pharmacy Review & Research.* 2015;5(1):15-23.
- Suresh Rewar. Design, development and evaluation of pulsatile drug delivery system of eprosartan mesylate for chronopharmacotherapy. *Asian Journal of Research in Biological and Pharmaceutical Sciences.* 2(4), 2014, 171 - 182.
- Babji Movva, Saritha M., Deepthi CH, Laxmankumar D, Srinivasrao Y. Design and Evaluation Core in Cup Pulsatile Tablet of Amlodipine Besylate for Early Morning Hypertension. *Int. J. Pharm. Sci. Rev. Res.,* 2013;23(1): 216-219.
- Borgaonkar PA, Bushetti SS, Najmuddin M Formulation and Evaluation of Pulsatile Drug Delivery System of MetoprololTartarate Using Core in Cup Tablet. *American Journal of Medicine and Medical Sciences.* 2012; 2(6):114-122.
- Nagaraju R, Sai Meera D, Rajesh K, Arvind VK , Venkateswarlu V. Core-in-cup Tablet Design of Metoprolol Succinate and its Evaluation for Controlled Release. *Curr Drug Discov Tech J* 2009; 6: 299-305.
- Harish Nairy M, Gulzar Ahmed M, Narayanacharyulu R, Satyanarayana D, Subrahmanayam EVS. Investigation and Comparison of Colon Specificity of Novel Polymer Kharaya Gum with Guar gum. *Pak. J. Pharm Sci* July 2010;23(3):259-265.
- Nagaraju R, Sai Meera D, Rajesh K, Venkata Arvind V, Venkateswarlu V. Core-in-Cup Tablet : Design of Metoprolol Succinate and its Evaluation for Controlled Release., *Current drug discovery technology.* 2009;6: 299-305.
- Desai K.G.H , Pramod Kumar T.M, Development and Evaluation of novel buccal adhesive core-in-cup tablets of Propranolol hydrochloride, *Indian journals of pharmaceutical sciences.* 2004; 66(4); 438-43.
- Raghavan CV, Muthulingam C, Jenita JA, Ravi TK. An in vitro and in vivo investigation into the suitability of bacterially triggered delivery system for colon targeting. *Chem Pharm Bull.* 2002;50(7):892-5.
- Yang L. Biorelevant dissolution testing of colon specific delivery systems activated by colonic microflora. *J Control Release.* 2008;125(2):77-86.