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EFFECT OF VARIOUS OSMOGENS ON DRUG RELEASE PROFILES OF SELF PORE FORMING OSMOTIC TABLETS OF AZATHIOPRINE

K. Ranjeeth Reddy*[1], M. Rajendar[2] and G. Kiran[2]

[1]Department of Pharmaceutics, Vaageswari College of Pharmacy, Karimnagar -505481 (A.P), India.

[2]Department of Pharmaceutics, St. John College of Pharmacy.

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***Correspondence for Author**
K. Ranjeeth Reddy
Department of Pharmaceutics, Vaageswari College of Pharmacy, Karimnagar - 505481 (A.P), India.

ABSTRACT

The purpose of this study was to formulate and evaluate self pore forming Osmotic ally controlled drug delivery system of azathioprine. Azathioprine is an oral anti-rheumatic agent which belongs to BCS class II with relatively short elimination half life of 3-5 hours. The main objective to formulate this system was to achieve zero order release for azathioprine. The present study was also aimed to develop a system that would reduce the frequency of dosing and thus increases patient compliance. Cellulose acetate was used as a film forming polymer. PEG 400 was used as plasticizers. PVP-K_{30} was used as pore forming agent. Acetone and isopropyl alcohol were used as solvent. Single and combination of Combinations of Mannitol, Lactose, sodium bicarbonate and potassium chloride were used as osmotic agents. Sodium lauryl sulphate was used as wicking agent. This system was developed in two stages: (a) formulation of core tablet and (b) coating of tablet core. Core tablets were evaluated for content uniformity, hardness and weight variation etc, while coated tablets were evaluated for percentage weight gain and in vitro release study. Effect of varying the concentration of pore forming agent on release rate was studied. Effect of various osmogens differing in osmotic pressure on release rate was also evaluated. Film was characterized by SEM studies.

KEYWORDS: Azathioprine, Potassium chloride, Mannitol, Lactose, Sodium bicarbonate, cellulose acetate, PVP-K_{30}, sodium lauryl sulphate.

INTRODUCTION

Conventional drug delivery systems have little or no control over the drug release, and effective concentration at the target site. This kind of dosing pattern may result in constantly changing, unpredictable plasma concentrations. The rate and extent of drug absorption from conventional formulations may vary greatly depending on the factors such as physico-chemical properties of the drug, presence of excipients, physiological factors such as presence or absence of food, pH of the gastro-intestinal tract (GI) and so on.[1] Studies of the controlled release of drugs for their extended and safe use have recently become an important field of research.[2] Among controlled-release devices, osmotic ally driven systems hold a prominent place because of their reliability and ability to deliver the contents at predetermined zero-order rates for prolonged periods.[3] Osmotic pumps (OP) are standard dosage forms for a constant-rate drug delivery. Preparation of self pore forming osmotic pump consists of the core containing the active material and a semi permeable membrane that coats the core, having a self pore forming material to produce orifices in the membrane in order to release the active material. When the system happens to be inside the gastrointestinal tract, the fluid enters the core through the membrane and dissolves the active material. The osmotic pressure generated in the core induces release of the drug in solution at a slow but constant rate. To gain the advantages of pH and agitation independent release performance leading to similar *in vitro/in vivo* delivery, osmotic ally active drug delivery systems have been extensively investigated.[4, 5] This approach can be for conversion of first order profile into zero order profile without altering the chemical structure.[6]

Azathioprine is a potent, anti-rheumatoid agent. It has a relatively short biological half-life (3-5) belongs to BCS II and it is used for the treatment of rheumatoid arthritis and organ graftings. This drug is administered for chronic disease in a controlled manner for long term use. The objective of the study was to develop osmotic ally controlled release tablets of azathioprine to be taken single per daily. In the current work, the formulation variables influencing the design of azathioprine core tablets were reported. Coating of the best achieved core formula (F10) with mixtures of cellulose acetate (CA) solution (2%, 3%, and 4%, w/v), polyethylene glycol 400 (PEG-400), in different ratios, was further investigated in an attempt to design self pore forming tablets with zero-order drug release kinetics.[7-9] Recently, osmotic tablets have been developed in which the delivery orifice is formed by the incorporation of a leachable component in the coating.[10, 11]

MATERIALS AND METHODS

Materials

Azathioprine was obtained from Raks Pharma,Vijaz,India, as a gift sample. It is a white a pale yellow odorless powder with melting point of 243.5^{o}C. Spray dried mannitol and Spray dried lactose were obtained as a gift from Indchem International, Mumbai, Sodium bicarbonate (Rishi Chemicals, Kolkatta) as gift sample and they were used as osmogens. Spray dried mannitol (Indchem) was used as diluent and osmogen. Avicel pH 101, Povidone, magnesium stearate and potassium chloride were purchased from Central Drug House, New Delhi and they were used as diluent, binder, lubricant, osmogen respectively. Cellulose acetate with 39.8% acetyl content was obtained from Eastman Chem., USA as a gift sample and it was used as semi permeable membrane. PVP (CDH) and PEG 400 (s. d. fine chem.) was used as pore former and plasticizer respectively. The other chemicals used were of analytical grade.

Methods

Preparation of core tablets

Core tablet formulae (F1–F10), each containing 100 mg of azathioprine, were prepared by direct compression using a multi punch tablet press machine, R&D (CEMAC, India) equipped with concave punches (12.0 mm). The each batch size is 100. The respective excipients were shown in Table no 1 including the drug (azathioprine), and osmogens (lactose, mannitol, potassium chloride, and sodium bicarbonate), and diluents (Avicel® PH101) were separately passed through sieve no.60. The sieved powders were mixed for 10 min using a pestle and mortar. Finally, the lubricants (magnesium stearate and talc) were added and gently mixed in poly bag for another 3 min with the previously blended powders. Accurate weights of 700 mg of each powder mixture were pressed in the tablet press machine to produce the desired core tablets. The tablet hardness was kept constant.[8]

Coating of Core tablets

The Core tablets were coated with 3% solution of cellulose acetate in acetone/isopropyl alcohol (80:10) mixture. PEG 400 was used as a plasticizer and PVP was used as pore former in semi permeable coating. Coating composition is given table no 2. Coating was carried out in non perforated coating pan (VJ Instruments Limited, Mumbai, India). Core tablets were sprayed with coating solution at following parameters: Pan RPM: 35-40, Inlet temperature: 45-50oC, Atomization pressure: 2-1.5 Kg/cm2, Spray rate: 3 ml/min. During coating run few

tablets were taken randomly and percentage weight gain was determined and coating was continued until desired weight gain was obtained on the tablets.[9] Coated tablets were dried at 50°C for 30 min in the same coating pan at 5 rpm to remove residual solvents.

Formulation Development

Osmotic tablet consist of core tablet coated with a rate controlling membrane. Tablet core consists of drug along with osmogen, and other conventional excipients to form the core compartment. The core tablet is surrounded by a membrane consisting of a semi permeable polymer and pore former cum plasticizer capable of improving film-forming properties of the polymers. The semi permeable membrane is permeable to aqueous fluids but substantially impermeable to the components of the core. During operation, the core compartment imbibes aqueous fluids from the surrounding environment across the membrane. The dissolved drug is released through the pores created after leaching of water soluble additive in the membrane.

Table no 1: List of components used in self pore forming osmotic tablets

Components (mg)	Formulation codes									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Azathioprine	100	100	100	100	100	100	100	100	100	100
Spray dried lactose	150			150			300			150
Spr. Mannitol		150		150	380	230				73
Pot. chloride			150					300		150
Sod. bicarbonate					150				300	150
Na.Laurylsulphate	-	-	-	-	14	14	21	21	21	21
PVP-K30	49	49	49	49	35	35	35	35	35	35
Micr.cry.cellulose	380	380	380	230	-	-	-	-	-	-

Note: Each formulation contains 7 mg and 14 mg of talc and magnesium stearate respectively.

Table No: 2.Coating composition for various batches (F1-F10)

Coating components	Formulation codes									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Cellulose acetate(gm)	3	3	3	3	3	3	3	3	3	3
PEG-400 (ml)	5	5	5	5	5	5	5	5	5	5
PVP-K30 (gm)	1	1	1	1	1	1	1	1	0.5	0.5
Acetone (ml)	75	75	75	75	75	75	85	85	85	85
Isopropyl alcohol (ml)	20	20	20	20	20	20	10	10	10	10
Total (ml)	100	100	100	100	100	100	100	100	100	100

RESULTS AND DISCUSSIONS

Post compressive parameters of core tablets

Prepared osmotic tablets of azathioprine of all the formulations (F1 to F10) were circular in shape with convex surfaces. Among all the formulations, the best formulations (F3, F7, F9 & F10) were evaluated for hardness, friability, weight variation and drug content, thickness and diameter. The results were summarized in table no 3. The drug content for all formulations ranged from 96.50 to 98.30 %, which is within the IP limit. For all formulations, % friability was less than 1% and sufficient hardness ranging from 8.0 to 9.5 Kg/cm^2. Tablets were evaluated for weight variation, thickness and diameter and the values were found to be within the IP limits.

Table no 3: Post compressive parameters for coated tablets

Parameters	Formulation Codes			
	F3	F5	1F9	F10
Weight variation*(mg)	705±7.4	712±5.5	702±9.4	705±6.5
Friability**	0.15±0.012	0.13±0.021	0.26±0.011	0.24±0.013
Thickness (mm)**	5.6±0.12	5.5±0.13	5.4±0.14	5.4±0.11
Diameter (mm)**	12.7±0.15	12.8±0.14	12.8±0.17	12.9±0.09
Hardness (Kg/cm2)***	9.2±0.3	9.0±0.4	8.9±0.5	9.1±0.6
Drug content***	96.5%	98.2%	97.5%	98.3%

All values are represented as mean ± standard deviation (n=10, **=5, ***=3)*

Effect of osmogens Concentration

To study the effect of osmogen concentration on drug release, formulations were prepared with different concentration of sodium bicarbonate, super tab and Mannogem and all other parameters of tablet kept constant. Quantities of osmogens were varied in range of 150 mg/tab to 300 mg/tab. By reducing the concentration of osmogens, dissolution rate of azathioprine decreases as explained in table no 4 and figure no 1. Therefore it is concluded that drug release from prepared tablet was done through osmotic pressure.

Table no 4: Effect of various osmogens on drug release

Time (Hrs)	Various ratios of osmogens (Drug: Osmogens)					
	Lactose		Mannitol		Sodium bicarbonate	
	1:1	1: 1.5	1: 1	1:1.5	1:1	1:1.5
0	0	0	0	0	0	0
2	3.84	7.88	3.94	9.68	5.69	8.33
4	5.6	14.77	6.57	13.16	11.08	19.69
6	9.48	23.57	9.81	15.93	17.76	28.49
9	15.19	32.29	11.68	25.15	22.2	38.62
12	23.72	44.21	16.39	38.25	28.3	49.64
18	35.31	68.75	22.23	52.11	38.49	72.48
24	48.97	88.39	38.19	75.2	55.6	88.02

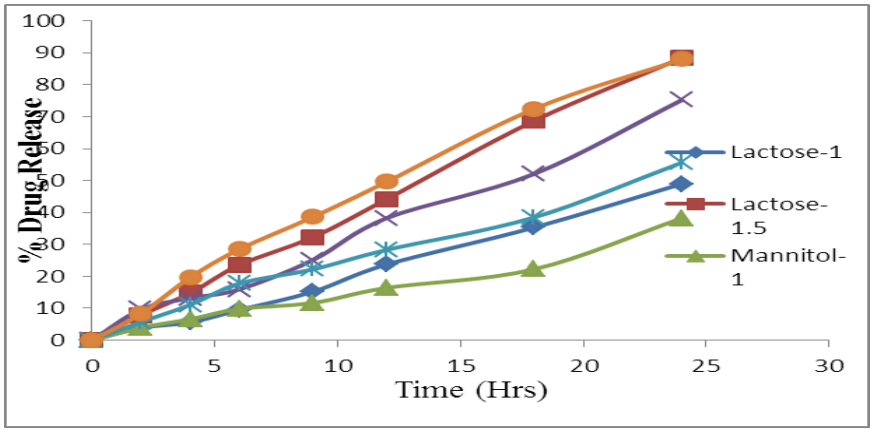


Figure no 1: Influence of osmogens concentration on drug release

Effect of sodium lauryl sulphate

To study the effect of sodium lauryl sulphate on drug release profiles of osmotic tablets of azathioprine, SLS was incorporated at 0%, 2%, 3% and 4% w/w of drug. During work I was observed that 4% w/w (F16) of SLS adhered/slicked to the punches and dies during compression due to moisture uptake from the environment. The results were shown in table no 5 and figure no 2.

Table no 5: Effect of sodium lauryl sulphate

Time (Hrs)	Various ratios of SLS (Drug:SLS)		
	1:0	1:2	1:3
0	0	0	0
2	3.53	8.44	7.88
4	6.65	12.38	14.77
6	11.65	17.81	23.57
9	15.52	23.5	32.29
12	19.46	27.5	44.21
18	25.11	35.51	68.75
24	32.65	47.5	88.39

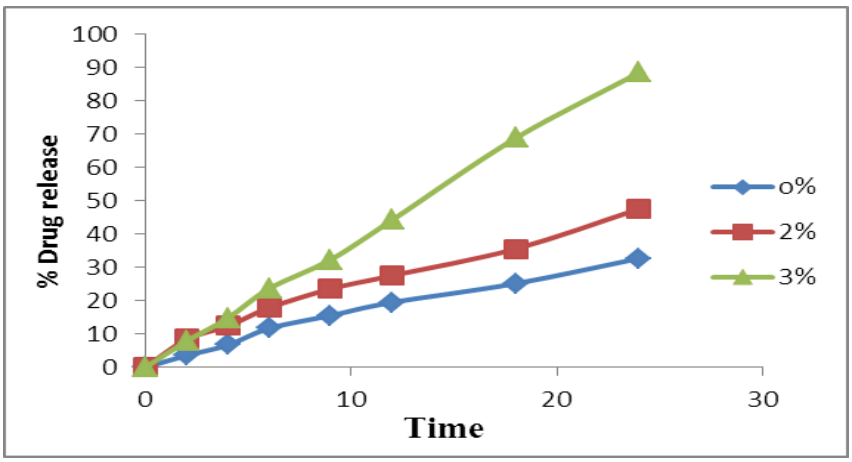


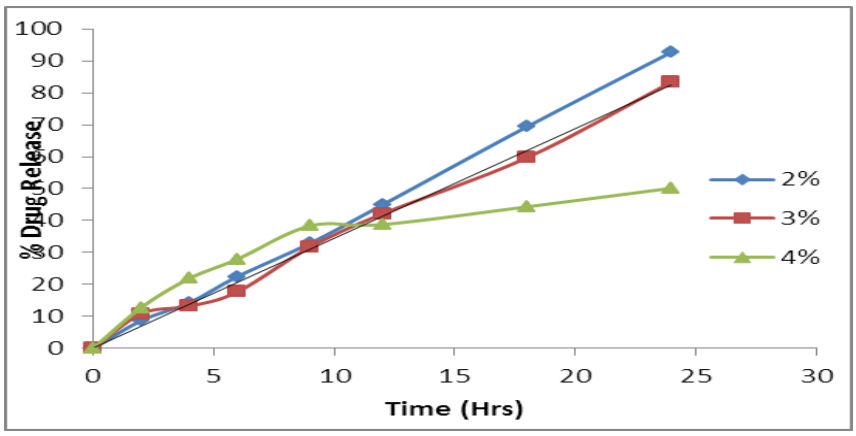
Figure no 2: Effect of sodium lauryl suphate on drug release studies.

Effect of concentration of pore former & weight gain

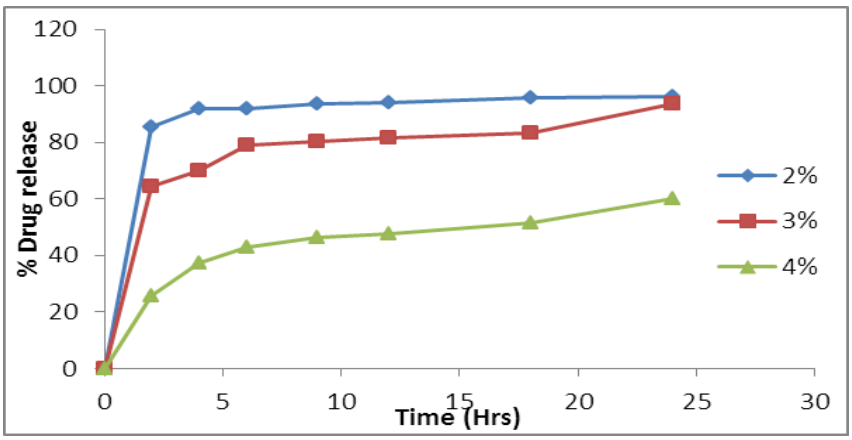
To study the effect of weight gain of the coating on drug release, core tablets of azathioprine were coated so as to get tablets with different weight gain (2, 3, 4% w/w). It clearly shows that drug release decrease with an increase in weight gain of membrane and increase with an increase in concentration of channeling agent. The results were shown in table no 6 and figure no 3.

Table no 6: Drug release profiles with different % weight gain (F10)

Time (Hrs)	0.5% channeling agent			1.0% channeling agent		
	2%	3%	4%	2%	3%	4%
2	8.75	10.92	12.86	85.32	64.30	25.62
4	14.35	13.23	23.95	91.84	69.87	37.48
6	22.56	17.77	28.01	92.08	79.05	43.06
9	32.93	31.74	35.39	93.82	80.20	46.54
12	44.93	42.11	38.77	94.20	81.60	47.64
18	69.39	59.71	44.34	95.70	83.15	51.38
24	92.74	83.40	50.17	96.32	93.57	60.31



A. With 0.5 % channeling agent



B. With 1% channeling agent

Figure no 3: Study the effect of concentration & percentage weight gain

Inference: *Drug release decrease with an increase in weight gain of membrane and increase with an increase in concentration of channeling agent.*

Study osmotic principle

The coated tablets were subjected for in vitro dissolution in 2 and 5 % solutions of potassium chloride solutions. It was clearly noted that the drug release was prevented as an increased amount of KCL in the dissolution media a explained in table no 7 and figure no 4.

Table no 7: Study Osmotic Principle (F9 -4%)

S. no	Time (Hr)	Distilled water	2% KCL	5% KCL
1	2	7.88±3.2	7.50±2.5	08.79±2.5
2	4	14.77±3.4	11.17±3.6	9.93±2.6
3	6	23.57±2.5	16.13±4.2	11.52±1.4
4	9	32.29±4.2	21.15±3.5	13.90±2.6
5	12	44.21±3.9	32.02±3.8	19.19±2.1
6	18	68.75±3.5	42.32±3.6	21.10±1.5
7	24	88.39±3.6	68.26±2.9	25.07±2.5

All values are represented as mean± standard deviation (n=3)

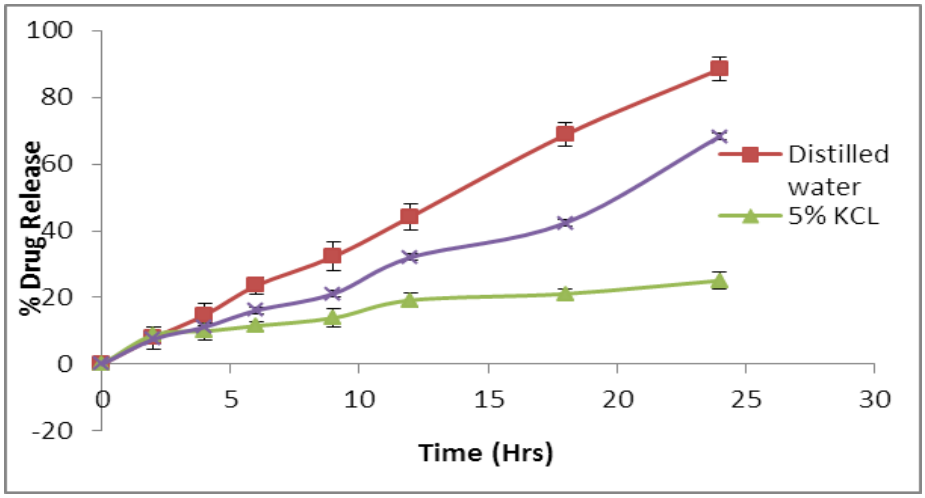


Figure no 4: Drug release profiles in various media

Inference: *Drug release was retarded /prevented at higher concentrations of KCL, due to less water potential in medium.*

Effect of plasticizers & channeling agent

To study effect of plasticizers & pore former on drug release studies, the core tablets were coated with PEG-400 & DBP, the drug release profiles summarized in table no 8 and figure no 5. It was observed that there was no drug release in absence of PVP.PEG-400 has shown best drug release when compared with DBP due to hydrophilic nature.

Table no 8: Effect of plasticizers for F3 (3%)

Time (Hr)	Plasticizers & pore former			
	PEG-400	DBP	PEG+PVP	DBP+PVP
2	3.96	1.05	6.08	2.68
4	4.38	1.58	17.5	3.70
6	5.16	1.97	24.05	9.88
9	5.47	2.46	35.76	12.06
12	6.13	3.31	48.46	15.42
18	8.39	4.74	69.11	16.27
24	10.95	8.51	94.65	20.92

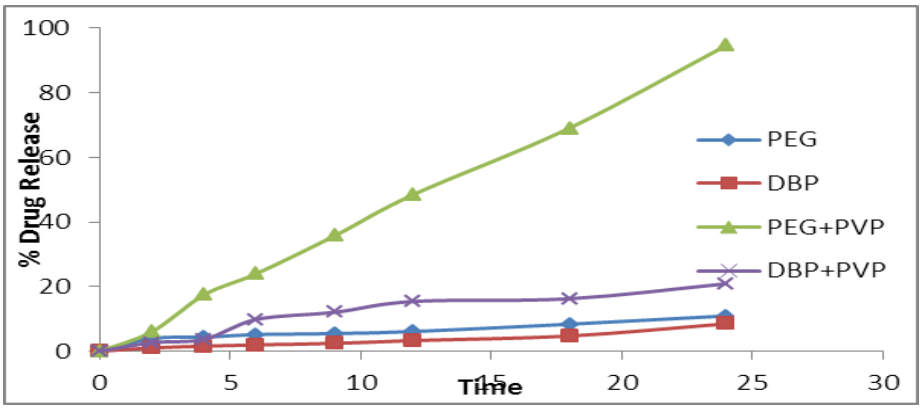


Figure no 6: Effect plasticizers & pore former

Inference: *Dibutyl Phthalate is retarding the drug release where as PEG-400 accelerate and there is no drug release in absence of channeling agent.*

Effect of pH

To study the effect of pH and assure a reliable performance of developed formulation independent of pH, release study of optimized formulation were conducted according to pH change method. The release media was 0.1N HCL, phosphate buffer (pH 6.8 Distilled water (pH 7.0). There is no significant difference observed in azathioprine release rate in different pH medium is explained in the table no 9 and figure no 7.

Table no 9: Effect of pH on drug release profiles for F3 (3%)

S.No	Time (Hr)	Distilled water	0.1 N HCL	6.8 pH P.B
0	0	0	0	0
1	2	6.08±2.1	5.44±1.5	4.56±1.5
2	4	17.5±4.5	9.59±3.2	12.03±2.2
3	6	24.05±3.6	27.06±3.6	32.05±3.4
4	9	35.76±4.2	40.36±3.1	40.89±3.6
5	12	48.46±3.5	54.12±3.1	47.68±4.2
6	18	69.11±4.5	74.54±2.5	66.21±3.4
7	24	94.65±2.6	96.65±2.1	89.79±4.9

All values are represented as mean± standard deviation (n=3)

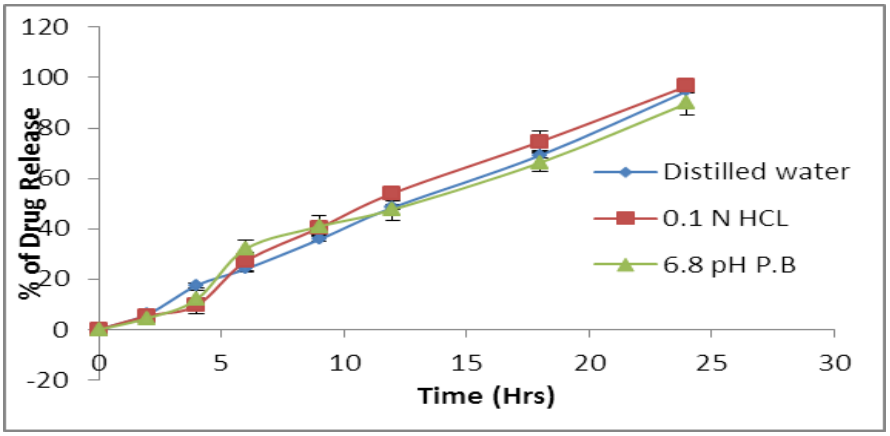


Figure no 7: effect of pH on drug release profiles

***Inference*:** *There was no significant effect of pH on drug release from the dosage form.*

Kinetics of drug Release

Based on all the results in *in-vitro* drug release, we came to know that these were good results among all the formulations. The release profiles were shown in below table no 10, 11 and figure no 8.

1. The 'r' values for zero order kinetics of F3, F7, F9 and F10 were 0.9970, 0.9983, 0.9880and 0.9985 respectively.
2. The 'r' values for first order of F3, F7, F9 and F10 were 0.9801, 0.9594, 0.9352 and 0.9583 respectively. The 'r' values indicate the drug release follows zero order.
3. The 'r' values of Higuchi diffusion was 0.9097, 0.8927, 0.9058and 0.8894 for formulation F3, F7, F9 and F10 respectively.
4. It suggests that the Zero order plots of all the formulations were fairly linear because 'r' values near about 1 in all the cases. So it confirms the drug release by osmosis mechanism follows zero order release and depends on time.
5. After the n value reaches 0.89 and above, the release can be characterized by case II and super case II transport, which means the drug release rate does not change over time and the release is characterized by zero-order release. The n value obtained from Peppas plot was found to be .952 for F10.

Table no 10: Regression coefficient for best formulations

Drug release orders	Formulation code			
	F5	F17	F19	F20
Zero	0.9970	0.9983	0.9880	0.9985
Higuchi	0.9097	0.8927	0.9058	0.8894
Peppas	0.9846	0.9980	0.9850	0.9937
First	0.9801	0.9594	0.9352	0.9583

Table no 11: kinetics of drug release

Time (Hrs)	Formulation codes and % weight gain			
	F3-3%	F7- 4%	F9-3%	F10-2%
2	6.08±2.1	7.88±1.2	8.33±1.5	8.75±1.6
4	17.5±4.5	14.77±2.4	19.69±2.6	14.35±2.6
6	24.05±3.6	23.57±2.5	28.49±2.5	22.56±1.9
9	35.76±4.2	32.29±2.2	38.62±2.9	32.93±3.1
12	48.46±3.5	44.21±2.9	44.64±2.6	44.93±.2.8
18	69.11±4.5	68.75±3.5	75.48±2.8	69.39±2.1
24	94.65±2.1	88.39±3.6	88.02±2.7	92.74±3.6

All values are represented as mean± standard deviation (n=3)

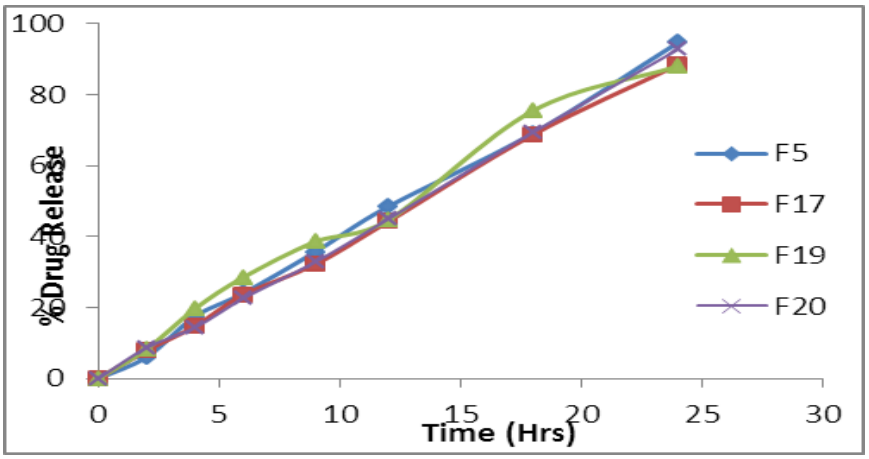
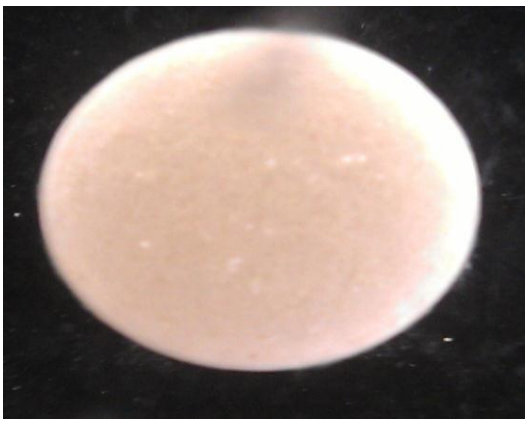


Figure no 8: Release kinetics for zero order

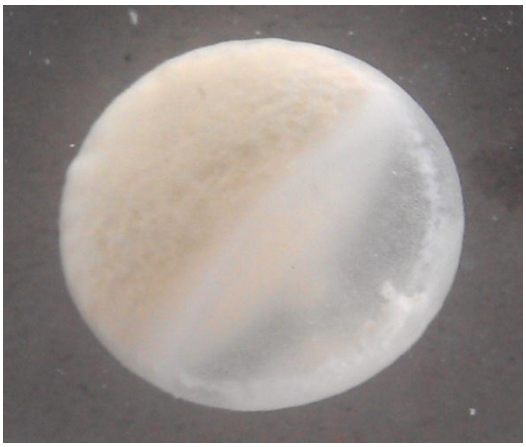
Snap shot studies

During *in-vitro* studies, snap shot were taken at 0, 2 12, 24 hrs as shown in figure no 9. The images reveals that the when intact tablets was placed in dissolution media, the tablet imbibe water from the surroundings into tablet core so there by increasing pressure in the core. Pore former slowly solubulizes in dissolution media then forms micopore in the membrane which results in the leaching out drug and excipients from the core in a controlled manner.

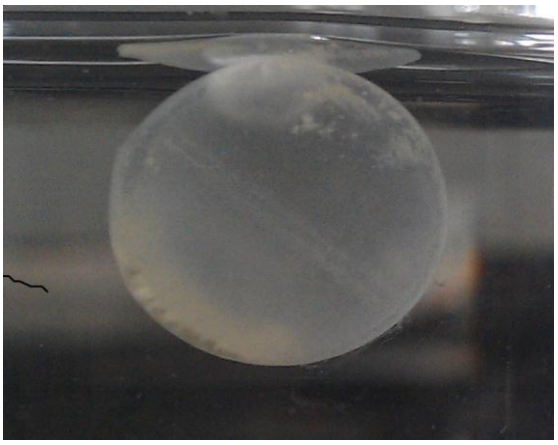
Intact



at 2 Hrs



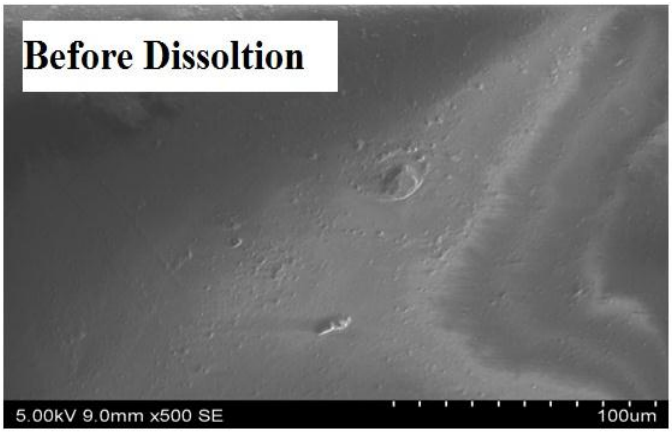
at 12 Hrs



at 24 Hrs

Scanning Electron Microscopy

Cellulose acetate (CA) membranes of optimized formulation, F20-2% (coat C-II), obtained before and after dissolution were studied by SEM. After 24-hour dissolution, the membrane clearly showed pores in range of 3 to 12 µm as shown in figure no 10 owing to dissolution of sorbitol. The leaching of PVP K_{30} from the membrane leads to formation of pores, and thus the release of drug takes place.



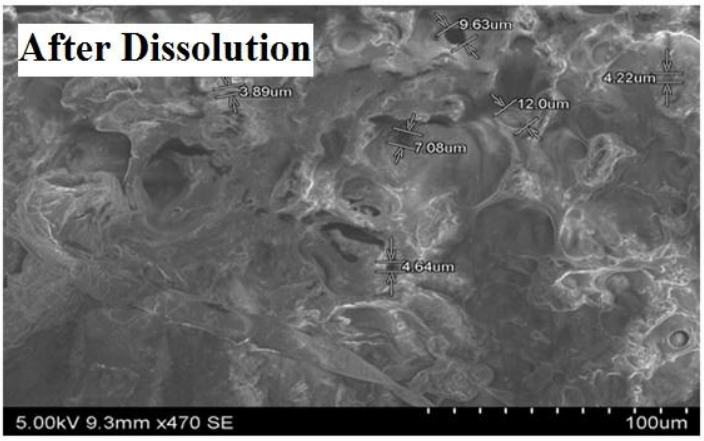


Figure no 10: Scanning electron photomicrographs

CONCLUSION

Controlled release formulations of azathioprine were developed based on osmotic technology. It is difficult to formulate the osmotic tablet of drugs having low solubility. Solubility of drug is required to increase to get desired profile. The drug release was increased as the levels of pore former and wicking agent is increases. The effect of different formulation variable was studied to optimize release profile. The release rate increased significantly as the increase of lactose, mannitol and sodium bicarbonate amount from 150 mg to 300 mg. In case of potassium chloride, the tablets were formed with imperfections as increased with the concentration. The drug release was increased with the mannitol as diluents where as decreased with avicel. Increasing in the coating weight gain from 1.5 to 4.5, there was a decrease in drug release rate. Based on results the functional key excipients was sodium lauryl sulphate. The release from developed formulations was independent of pH. The drug release from the developed formulation was inversely proportional to the osmotic pressure of the release media and SEM images confirming osmotic pumping to be the major mechanism of drug release.

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REFERENCES

1. Sapna N, Makhija, Pradeep R. Vavia. (Controlled porosity osmotic pump based controlled release systems of pseudoephedrine). Journal of Controlled Release, 2003; 89: 5-18.
2. Chien YW. Novel drug delivery systems. 2nd ed. New York; Marcel Dekker.139: 96.
3. Sjaclyn Anderson, Liron Caplan, Jinoos Yazdany, Mark L, Robbins, Tuhina Neogi, Kaleb Michaud, Kenneth G. Saag, James R. O'dell, And Salahuddin K. Rheumatoid Arthritis Disease Activity Measures: American College Of Rheumatology, Recommendations For Use In Clinical.
4. Prajapati H.M, Prajapati S. T, Patel C.N. (A Review on Recent Innovation In Osmotically Controlled Drug Delivery System). IJPRBS, 2012; 1(3): 158-194.

5. Hardik Prajapathi, M. M. Patel. (Formulation and Evaluation of Controlled Porosity Osmotic Drug Delivery System of Carvedilol Phosphate). JPSBR, 2012; 2(2): 77-82.
6. McClelland GA, Sutton SC, Engle K, Zentner GM. (The solubility-modulated osmotic pump: in vitro/in vivo release of diltiazem hydrochloride). Pharm. Res, 1991; 8: 88–92.
7. Panchaxari M. Dandagi, Navik V, Koradia, Anand P. Gadad And Sowjanya P. (Fabrication and *in vitro* evaluation of porous osmotic pump based controlled drug delivery of metaprolol succinate). Int J Pharm Pharm Sci, 2012; 4(3): 697-704.
8. Geeta M, Pateland Jayendra, D. Patel. (Single Core Osmotic Pump (SCOP): Development of Single Layer Osmotic controlled release tablet for poorly soluble drug). Journal of Pharmaceutical Technology & Drug Research, 2012; 1-15.
9. Mahalaxmi.R, Phanidhar Sastri, Ravikumar, Atin Kalra, Pritam Kanagale.D, Narkhede R. (Enhancement of Dissolution of Glipizide from Controlled Porosity Osmotic Pump Using A Wicking Agent And ASolubilizing Agent). Int J PharmTech Res, 2009; 1(3): 705-711.
10. Sudeesh Edavalath, Shivan, K Kalyani, H .K. Prakasam, B Prakash Rao and Goli. (Formulation development and optimization of controlled porosity osmotic pump tablets of diclofenac sodium). Int J Pharma Pharma Sci, 2011; 3(1): 80-87
11. Ahmed Abd Elbary, Mina Ibrahim Tadros and Ahmed Adel Alaa Eldin. (Development and *In Vitro* / *In Vivo* Evaluation of Etodolac Controlled Porosity Osmotic Pump Tablets). AAPS PharmSciTech, June 2011; 12(2): 485-495.