IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

A STUDY ON FORMULATION AND EVALUATION OF DIPYRIDAMOLE FLOATING TABLETS BY USING DIFFERENT POLYMERS

M.Venu[1], K.Balamurugan[2], D.Jayasri[3], V.Deepka kumar[3], B.Ashok[3], Ch.Sri Lakshmi[3], N.Uday kiran[3]

1. **Asst.professor, Department of Pharmacy, Lydia college of Pharmacy,Nh-5, Ethakota,East Godavari, Ravulapalem, Andhra Pradesh 533238.**
2. **Professor, Department of Pharmacy, Annamalai University, Annamalai Nagar, Tamilanidu.**
3. **Asst.professor, Department of Pharmacy, Lydia college of Pharmacy,Nh-5, Ethakota,East Godavari, Ravulapalem, Andhra Pradesh 533238.**

ABSTRACT:

In the present research work gastro retentive floating matrix formulation of Dipyridamole by using various hydrophilic polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various natural polymers. The formulation blend was subjected to various preformulation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulations prepared by using Xanthan gum were unable to produce desired drug release, they were unable to retard drug release up to 12 hours. The formulations prepared with HPMC K15 M retarded the drug release up to 12 hours in the concentration of 200 mg (F6). The formulations prepared with Guar gum also retarded the drug release for more than 12 hours. Hence, they were not considered. The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed Higuchi mechanism of drug release.

Keywords: Dipyridamole, Guar gum , Xanthan gum ,HPMC K15 M and Floating tablets.

INTRODUCTION ON FLOATING DRUG DELIVERY SYSTEMS

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage forms. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process.

Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drugs for rapid absorption. These immediate release dosage forms have some limitations such as;

1) Drugs with short half-life require frequent administration, which increases the chances of missing dose of drug leading to poor patient compliance.

2) A typical peak-valley plasma concentration-time profile is obtained which makes it difficult to attain steady state condition.

3) The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the C_{SS} values fall or rise beyond the therapeutic range.

4) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs. In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery systems that could revolutionize methods of medication and provide a number of therapeutic benefits.

Controlled Drug Delivery Systems:

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a

tissue.Controlled drug delivery or modified drug delivery systems are conveniently divided into four categories.

1. Delayed release
2. Sustained release
3. Site-specific targeting
4. Receptor targeting

More precisely, Controlled delivery can be defined as: -

- Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.
- Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.
- Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.
- Provide a physiologically/therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/ therapeutic needs of the body.

1.2 Advantages of Controlled Drug Delivery System:

1. Avoid patient compliance problems.
2. Dosage frequency was reduced

a. eliminate local side effects

b. Minimize or eliminate systemic side effects

c. Obtain less potentiation or reduction in drug activity with chronic use.

d. Minimize drug accumulation with chronic dosing.

3. Improve efficiency in treatment

a. Cures or controls conditions more promptly.

b. Improves control of condition i.e., reduced fluctuation in drug level.

c. Improves bioavailability of some drugs.

d. Make use of special effects, e.g. Sustained-release aspirin for morning relief of arthritis by dosing before bedtime.

e. Economy i.e. reduction in health care costs. The average cost of treatment over an extended time period may be less, with less frequency of dosing, enhanced therapeutic benefits and reduced side effects. The time required for health care personnel to dispense and administer the drug and monitor patients is also reduced.

1.3 Disadvantages:

1) Systemic availability in comparison to conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.

2) Poor in vitro – in vivo correlation.

3) Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient and thus, increased risk of toxicity.

4) Retrieval of drugs are difficult in case of toxicity, poisoning or hypersensitivity reactions.

5) Reduced potential for dosage adjustment of drugs normally administered in varying strengths.

1.4 Oral Controlled Drug Delivery Systems:

Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either local or systemic action.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage form (solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology. Therefore, the scientific framework required for the successful development of oral drug delivery systems consists of basic understanding of

(i) Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug.

(ii) the anatomic and physiologic characteristics of the gastrointestinal tract.

(iii) physicochemical characteristics and the drug delivery mode of the dosage form to be designed.

The main areas of potential challenge in the development of oral controlled drug delivery systems are: -

- Development of a drug delivery system: To develop a viable oral controlled release drug delivery system capable of delivering a drug at a therapeutically effective rate to a desirable site for duration required for optimal treatment.
- Modulation of gastrointestinal transit time: To modulate the GI transit time so that the drug delivery system developed can be transported to a target site or to the vicinity of an absorption site and reside there for a prolonged period of time to maximize the delivery of a drug dose.
- Minimization of hepatic first pass elimination: If the drug to be delivered is subjected to extensive hepatic first-pass elimination, preventive measures should be devised to either bypass or minimize the extent of hepatic metabolic effect.

Conventional oral controlled dosage forms suffer from mainly two adversities. The short gastric retention time (GRT) and unpredictable gastric emptying time (GET). A relatively brief GI transit time of most drug products impedes the formulation of single daily dosage forms.

Altering the gastric emptying can overwhelm these problems. Therefore, it is desirable to formulate a controlled release dosage form that gives an extended GI residence time.

Extended-release dosage forms with prolonged residence time in the stomach are highly desirable for drugs.

1. They are locally active in the stomach.
2. They have an absorption window in the stomach or in the upper small intestine.
3. They are unstable in the intestinal or colonic environment.
4. Have low solubility at high pH values.

1.5 Gastroretentive DosageForm (GRDF):

It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in the stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDFs or GRDS).GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form.

Dosage form with prolonged GRT, i.e. gastro retentive dosage form (GRDF), will bring about new and important therapeutic options such as –

1) This application is especially effective in sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. To override this problem, erodible, gastro retentive dosage forms have been developed that provide continuous, controlled administration of sparingly soluble drugs at the absorption site.

2) GRDFs greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentration at the gastric mucosa. (For e.g. Eradicating Helicobacter pylori from the sub mucosal tissue of stomach) making it possible to treat stomach and duodenal ulcers, gastritis and esophagitis, reduce the risk of gastric carcinoma and administer non-systemic controlled release antacid formulations (calcium carbonate).

3) GRDFs can be used as carriers for drugs with so-called absorption windows. These substances for e.g. antiviral, antifungal and antibiotic agents (Sulphonamides, Quinolones, Penicillin's, Cephalosporins, aminoglycosides, Tetracycline etc.) are taken up only from veryspecific sites of the GI mucosa.

METHODOLOGY:

Analytical method development:

a) **Determination of absorption maxima:**

A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCl UV spectrum and was taken using a Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

b) **Preparation calibration curve:**

100mg of Dipyridamole pure drug was dissolved in 100ml of 0.1N HCl (stock solution)10 ml of solution was taken and make up with 100ml of 0.1N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain a series of dilutions Containing 1,2,3,4 and 5µg/ml of Dipyridamole per ml of solution. The absorbance of the above dilutions was measured at 266 nm by using UV- Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which is determined by least-square linear regression analysis.

Formulation development of Tablets:

All the formulations were prepared by direct compression. The compression of different formulations is given in Table 6.3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Dipyridamole. Total weight of the tablet was considered as 6500mg.

Procedure:

1) Dipyridamole and all other ingredients were individually passed through sieve no 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using a direct compression method.

Optimization of Sodium bicarbonate concentration:

Sodium bicarbonate was employed as an effervescent gas generating agent. It helps the formulation to float. Various concentrations of sodium bicarbonate were employed; floating lag time and floating duration were

observed. Based on that the concentration of sodium bicarbonate was finalized and preceded for further formulations.

S.No	Excipient Name	EF1	EF2	EF3
1	Dipyridamole	300	300	300
2	HPMC K15M	150	150	150
4	$NaHCO_3$	75	90	105
5	Mg.Stearate	6	6	6
5	Talc	6	6	6
7	MCC pH 102	Q.S	Q.S	Q.S
	Total weight	600	600	600

All the quantities were in mg.

Table 7.3: Optimization sodium bicarbonate concentration

Based on the floating lag time and floating duration the concentration of sodium bicarbonate was optimized.

Table 7.4: Formulation composition for floating tablets

Formulation No.	**Dipyridamole**	**Xanthan gum**	**HPMC K15M**	**Guar gum**	**$NaHCO_3$**	**Mag. Stearate**	**Talc**	**MCC pH 102**
F1	300	100	-----	-----	90	6	6	QS
F2	300	150	-----	-----	90	6	6	QS
F3	300	200	-----	-----	90	6	6	QS
F4	300	-----	100	-----	90	6	6	QS
F5	300	-----	150	-----	90	6	6	QS

F6	300	-----	200	-----	90	6	6	QS
F7	300	-----	-----	100	90	6	6	QS
F8	300	-----	-----	150	90	6	6	QS
F9	300	-----	-----	200	90	6	6	QS

All the quantities were in mg, Total weight is 600 mg.

Evaluation of post compression parameters for prepared Tablets

The designed compression tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. Not more than two of the individual weights deviate

from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Average weight of tablet (mg) (I.P)	Average weight of tablet (mg) (U.S.P)	Maximum percentage difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

Table 7.5: Pharmacopoeial specifications for tablet weight variation

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet.

The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness:

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability:

It measures the mechanical strength of tablets. Roche Friabilator was used to determine the friability by following procedure. Pre-weighed tablets were placed in the Friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as % Friability = [(W1-W2) / W] × 100 Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

Determination of drug content:

Both compression-coated tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Meloxicam were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

In vitro Buoyancy studies:

The in vitro buoyancy was determined by floating lag time, and total floating time. (As per the method described by Rosa et al) The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT).

***In vitro* drug release studies**

Dissolution parameters:

Apparatus	--	USP-II, Paddle Method Dissolution Medium	--	0.1 N HCl
RPM	--	75		
Sampling intervals (hrs)	--	0.5,1,2,3,4,5,6,7,8,10,11,12 Temperature	--	37°c ± 0.5°c

As the preparation was for floating drug release given through oral route of administration, different receptor fluids are used for evaluation of the dissolution profile.

Procedure:

900ml 0f 0.1 HCl was placed in the vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and the vessel was covered. The apparatus was operated for 12 hours and then the medium 0.1 N HCl was taken and the process was continued from 0 to 12 hrs at 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed spectrophotometrically at 266 nm using UV-spectrophotometer.

RESULTS AND DISCUSSION:

The present study was aimed at developing gastro retentive floating tablets of Dipyridamole using various natural polymers. All the formulations were evaluated for physicochemical properties and in vitro drug release studies.

1.1. Analytical Method

Graphs of Dipyrridamolewas taken in Simulated Gastric fluid (pH 1.2) at 266 nm.

Table 8.1: Observations for graph of Dipyridamole 0.1N HCl (266 nm)

Conc [µg/l]	Abs
1	0.131
2	0.232
3	0.347
4	0.459
5	0.629

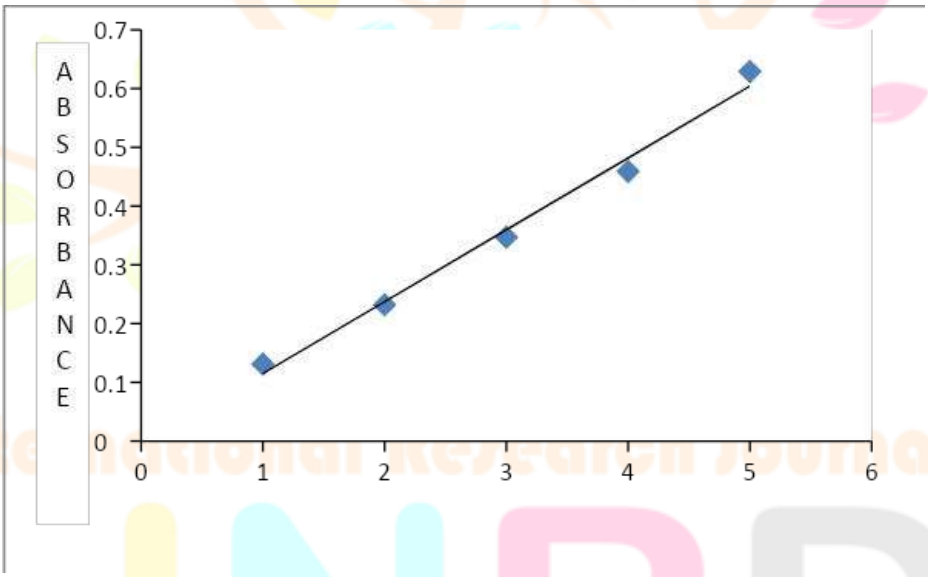

Figure 8.1: Standard graph of Dipyridamole in 0.1N HCl

1.2. Drug – Excipient compatibility studies Fourier Transform-Infrared Spectroscopy:

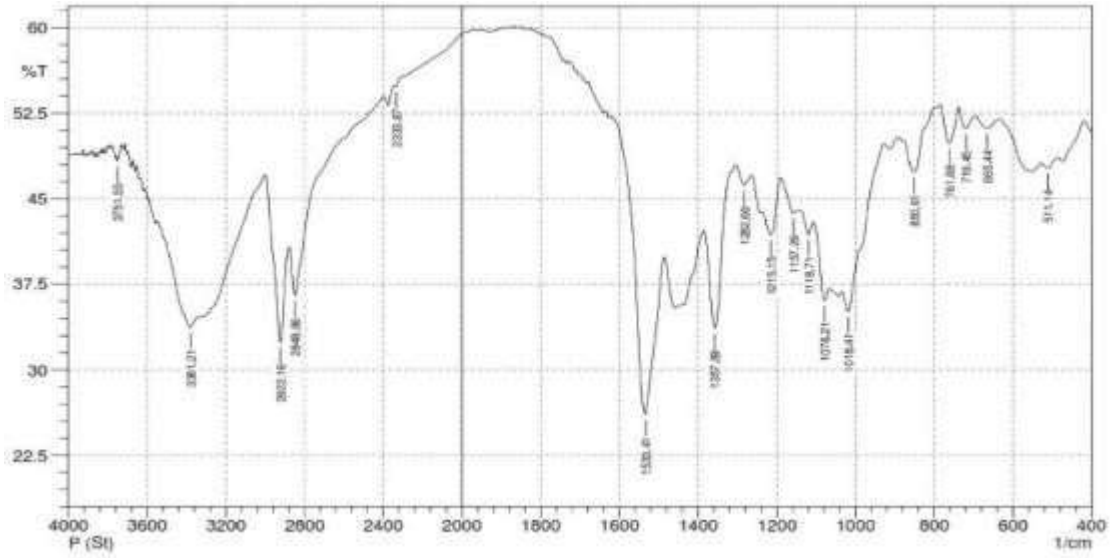

Figure 8.2: FT-TR Spectrum of Dipyridamole pure drug

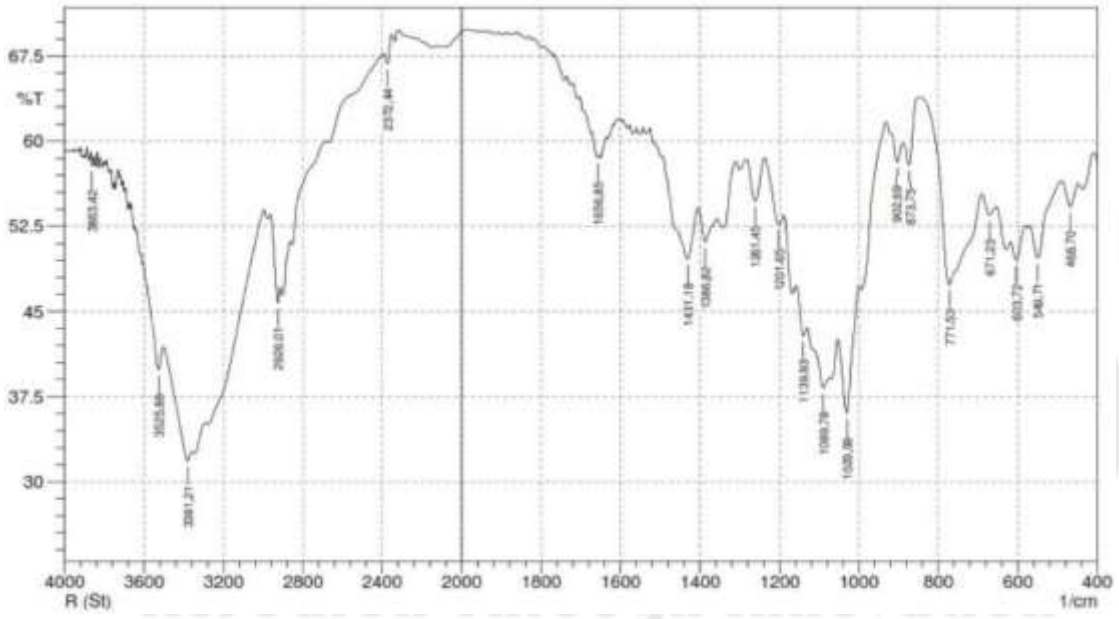

Figure 8.3: FT-IR Spectrum of Optimised Formulation

From the results of FTIR studies it was evident that the drug and excipients do not have any interactions.

1.3. Preformulation parameters of powder blend

Formulatio n Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	26.01	0.49±0.07	0.57±0.01	16.21±0.06	0.86±0.06
F2	24.8	0.56±0.06	0.62±0.05	16.87±0.05	0.98±0.05
F3	22.74	0.52±0.03	0.68±0.07	17.11±0.01	0.64±0.03
F4	25.33	0.54±0.04	0.64±0.08	17.67±0.08	1.12±0.04
F5	26.24	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08
F6	26.12	0.56±0.05	0.66±0.06	17.65±0.09	1.06±0.09
F7	27.08	0.58±0.06	0.69±0.04	16.43±0.05	0.76±0.03
F8	25.12	0.48±0.05	0.57±0.02	17.97±0.02	1.15±0.09
F9	25.45	0.54±0.08	0.62±0.03	17.54±0.09	1.17±0.02

Table8.2: Preformulation parameters of blend

Tablet powder blend was subjected to various preformulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43±0.07 to 0.58±0.06 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which show that the powder has good flow properties. All the formulations have shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

1.4. Optimization of sodium bicarbonate concentration:

Three formulations were prepared with varying concentrations of sodium bicarbonate. The formulation containing sodium bicarbonate in 75mg concentration showed less floating lag time of 4 min and the tablet was in floating condition for more than 12 hours.

1.5. Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the tablets.

Formulation code	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floatin g lag time (min)
F1	612.5	4.5	0.52	4.8	99.76	4.0
F2	605.4	4.2	0.54	4.9	99.45	4.2
F3	598.6	4.4	0.51	4.9	99.34	4.5
F4	610.6	4.5	0.55	4.9	99.87	4.1
F5	609.4	4.4	0.56	4.7	99.14	4.0
F6	610.7	4.2	0.45	4.5	98.56	4.4
F7	602.3	4.1	0.51	4.4	98.42	4.5
F8	601.2	4.3	0.49	4.7	99.65	4.6
F9	598.3	4.5	0.55	4.6	99.12	4.7

8.3. Invitro quality control parameters for tablets

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

1.6. *In-Vitro* Drug Release Studies

Table 8.4: Dissolution Data of Dipyridamole Tablets Prepared With Xanthan gum In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)		
	F1	F2	F3
0.5	21.73	19.52	21.53
1	60.23	37.47	28.94
2	84.9	60.93	37.89
3	95.873	65.85	45.7

4	94.873	75.54	56.38
5		89.55	61.2
6		98.6	68.06
7			72.52
8			78.88
9			86.6
10			90.09
11			95.57

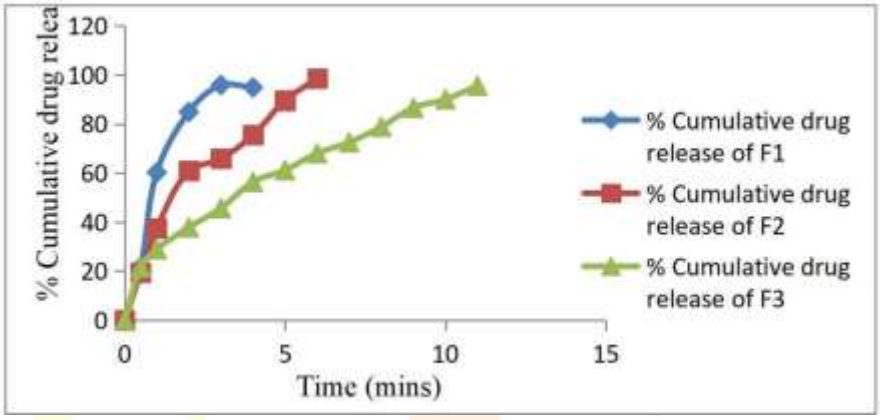

Fig 8.4: Dissolution profile of Dipyrridamole floating tablets (F1, F2, F3 formulations).

Table 8.5: Dissolution Data of Dipyridamole Tablets Prepared With HPMC K15M In Different Concentrations

TIME (hr)	**CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)**		
	F4	**F5**	**F6**
0.5	19.4	19.42	20.62
1	36.2	29.73	27.86
2	54.1	35.63	38.35
3	70.0	45.04	43.45
4	89.2	59.25	47.8

5	95.	62.35	55.28
6		75.41	60.24
7		85.85	68.73
8		94.8	71.34
9			79.52

10			82.17
11			89.75
12			98.21

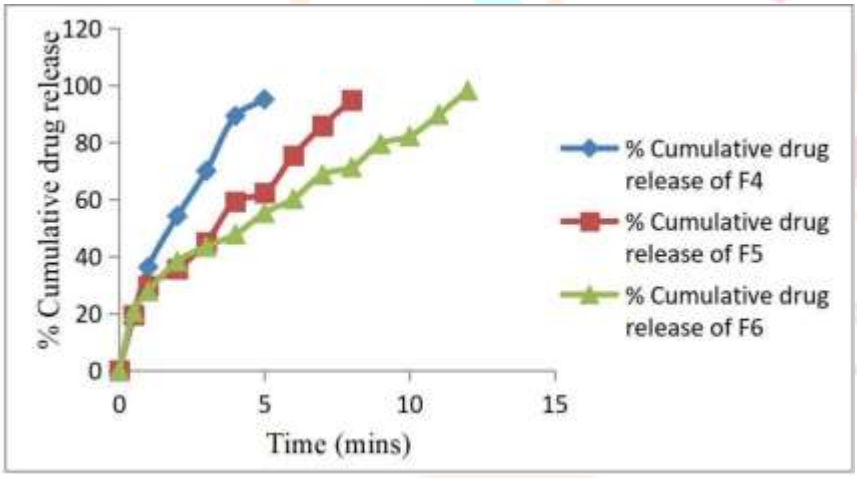

Fig 8.5: Dissolution profile of Dipyrridamole floating tablets (F4, F5, F6 formulations).

Table 8.6: Dissolution Data of Dipyridamole Tablets Prepared With Guar Gum In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)		
	F7	F8	F9
0.5	19.81	20.8	14.2
1	30.02	28.0	19.8
2	35.7	36.4	29.1
3	45.32	41.6	36.6
4	49.25	48.1	45.3
5	57.28	54.8	53.0

6	60.92	59.89	59.13
7	69.08	65.53	63.63
8	70.44	69.43	69.71
9	78.22	74.83	75.34
10	80.9	79.98	79.27
11	88.83	85.52	82.86
12	93.9	89.65	86.97

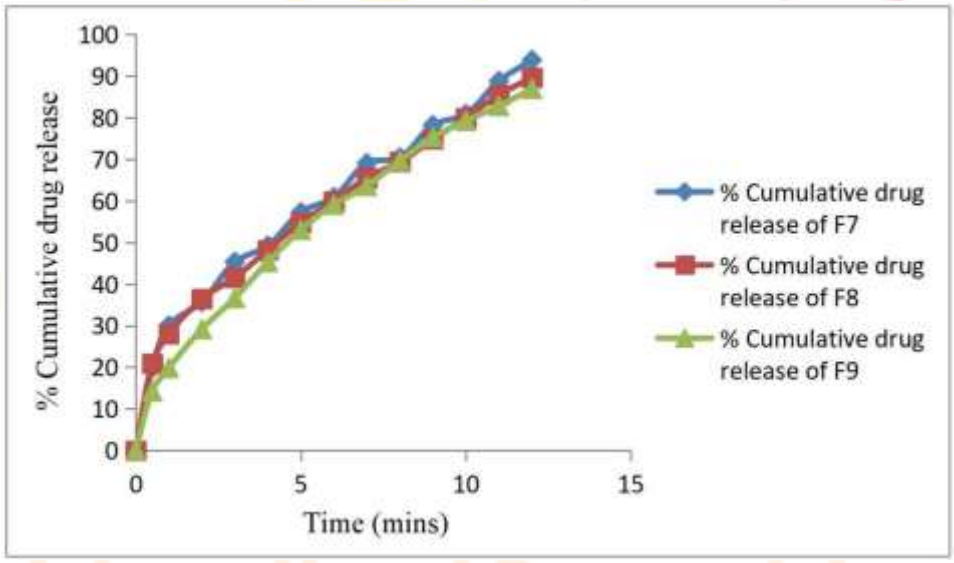

Fig 8.6: Dissolution profile of Dipyrridamole floating tablets (F7, F8, F9 formulations)

From the dissolution data it was evident that the formulations prepared with Xanthan gum as polymer were unable to retard the drug release up to desired time period i.e., 12 hours.

Whereas the formulations prepared with HPMC K15M retarded the drug release in the concentration of 200 mg showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 98.21 % in 12 hours (Formulation F6) with good floating lag time and floating buoyancy time.

The formulations prepared with Guar gum showed more retardation even after 12 hours they were not shown total drug release. Hence they were not considered.

Conclusion: In the present research work gastro retentive floating matrix formulation of Dipyridamole by using various hydrophilic polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different

concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various natural polymers. The formulation blend was subjected to various preformulation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulations prepared by using Xanthan gum were unable to produce desired drug release, they were unable to retard drug release up to 12 hours. The formulations prepared with HPMC K15 M retarded the drug release up to 12 hours in the concentration of 200 mg (F6). The formulations prepared with Guar gum also retarded the drug release for more than 12 hours. Hence, they were not considered. The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed Higuchi mechanism of drug release.

BIBLIOGRAPHY:

1. Leon Lachman, Herbert A. Liberman, the Theory and Practice of Industrial Pharmacy: P.293-302.

2. Robinson Jr, Lee V.H.L, Controlled drug delivery: Fundamentals and Applications, 2nd edn. Marcel Dekker, New York: (1978) P.24-36.

3. Brahmankar D.M, Jaiswal S.B, Biopharmaceutics and Pharmacokinetics a treatise, 1st ed. Vallabh prakashan; New Delhi: (1995) P.64-70.

4. Chein Y.W, Novel Drug Delivery Systems, 2nd ed.: Marcel Dekker; New York: (1992) P.4-56.

5. Ansel, Pharmaceutical Dosage form and Drug Delivery System, Lipincott, 7th edition: P. 553.

6. Gennaro R.A. Remington, The Science and Practice of Pharmacy., 20th ed. New York: Lippincott Williams: (2000) P.1045.

7. Banker G.S, Rhodes C.T, Modern Pharmaceutics. 3rd ed. Marcel Dekker, New York: (1996) P.678-721.

8. Vyas S.P, Khar R.K, Controlled Drug Delivery: Concepts and Advances, 1st ed. Vallabh prakashan, New Delhi: (2002) P.345-376.

9. P.G. Yeole, Floating Drug Delivery System: Need and Development, Ind. J. Pharm Sci., (2005): 67(3);

265-272.

10. Shweta Arora, Floating Drug Delivery: A Review, AAPS Pharmscitech., (2005): 47(11); P.268-272.

11. Libo Yang, A New Intragastric Delivery System for the Treatment of H. Pylori associated with gastric ulcers, Elsevier J. of controlled release., Apr (1999): 34 (5); P. 215-222.

12. Ross and Wilson, Anatomy Physiology and Health Education. 9th ed. Churchill Livingstone, P. 295-311.

13. Wilson K.R.W, Waugh A. Anatomy and physiology in Health and Illness, 9th ed. Churchill Livingstone: London: (1996). P. 342-345.

14. Garima Chawla, Gupta, Pharmaceutical technology, July (2003): 23(9); P.39-48.

15. Desai S, Bolton S. a Floating Controlled Release System: In-vitro and In-vivo evaluation, J. Pharm. Res., (1993): 10; P.1321-1325.

16. Garg S, Sharma S. Gastroretentive Drug Delivery Systems, Pharmatech, (2003): P.160- 164.

17. Dr. Jose, Khalid Shah, Gastroretentive Drug Delivery System, Business brief, Pharmtech., (2003) P. 165-173. Deshpande A.A, Shah N.H, Rhodes C.T, Development of a Novel Controlled Release System for Gastric Retention, J. Pharm. Res., (1997): 14(6); P. 815-819.