ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at: www.jgpt.co.in

RESEARCH ARTICLE

Development and Evaluation of Dipyridamole Multi Unit Floating Mini-Tablets

Kotharapu Rama Koteswararao*, Lankalapalli Srinivas

Department of Pharmaceutics, GITAM Institute of Pharmacy, Visakhapatnam, Andhra Pradesh, India.

***Corresponding Author: Kotharapu Rama Koteswararao**

Abstract

The objective of the present work was to formulate and to characterize multi unit floating drug delivery system of Dipyridamole to increase the bioavailability and sustain the drug release properties up to 8 h with more predictable drug release kinetics that avoids all or nothing emptying effect. Dipyridamole floating mini-tablets were prepared by effervescent approach with melt granulation and direct compression techniques alone and in combination using Hydroxypropyl methylcellulose (HPMC) K100M and Compritol 888 ATO at different concentrations (20%, 30% and 40% w/w) alone and in combination. Evaluations were carried out on physical parameters, floating behavior and influence of type of polymer on drug release rate of prepared mini tablet formulations. All the formulations were subjected to various quality control and *in-vitro* dissolution studies and corresponding dissolution data were fitted to popular release kinetic equations in order to evaluate release mechanisms and kinetics. All the dipyridamole floating mini tablet formulations followed zero order kinetics. As per Korsmeyer-Peppas equation, the release exponent "n" ranged 0.619-0.748 indicating that drug release from all the formulations was by non-Fickian diffusion mechanism. Based on the results, dipyridamole floating mini tablets prepared by employing combination of 15% w/w HPMC K100M and 15% w/w Compritol 888 ATO offered desired in-vitro floating time and drug dissolution profile.

Keywords: *Bioavailability, Dipyridamole, Floating mini-tablets, Release kinetics, Sustained release.*

Introduction

Oral controlled release drug delivery systems with ability to retain in the stomach are called gastro-retentive drug delivery system (GRDDS) which are aimed to enhance drug therapy with or without targeted action by prolonging the gastric residence time after oral administration [1].

The controlled gastric retention of the formulation may be achieved by the various approaches such as floatation, mucoadhesion, sedimentation, expansion and modified shape systems. Among the various approaches, floating drug delivery system (FDDS) promises to be a potential approach for prolonged gastric retention to improve solubility, reduces drug waste thereby improves bioavailability for the drugs that are less soluble in a high pH environment. FDDS offer the most effective and rational protection against early and random gastric emptying compared to the other methods proposed for prolonging the gastric residence time of solid dosage forms [2].

Most of the floating systems previously reported are single unit systems such as tablets and capsules. However, the problems such as all or nothing emptying of single unit floating dosage forms made them unreliable and irreproducible in prolonging the gastric residence time, which led to the development of multiple unit floating systems [3].

Multiple unit floating drug delivery systems, such as mini-tablets with diameter of 3-6mm, show several advantages over single unit system, which include avoiding all or nothing emptying, more predictable drug release kinetics, less chance of localized mucosal damage and administration of units with different release profiles or containing incompatible substance. Mini tablet have the advantages of both tablets and pellets and shows more reliable dissolution profiles than

single units, which means better bioavailability with more and even absorption of the drugs. In addition, they offer dosage forms of equal dimensions and weight with smooth regular surface that could be obtained in a reproducible and continuous way. Like other multiple unit systems, multiple mini-tablets can be filled into hard gelatin capsules that release these subunits after disintegration [4, 5].

Dipyridamole is a pyrimidopyrimidine derivative with vasodilator and anti-platelet properties. The mechanism of action of dipyridamole as an antiplatelet agent involves increased intracellular cyclic adenosine monophosphate (cAMP) which inhibits the platelet shape change [6]. Dipyridamole is a BCS class II drug having low solubility and high permeability.

It is soluble at low pH but insoluble in high pH (i.e. alkaline ph of small intestine) and the oral bioavailability is 37-66% with short (40min) biological half life. The recommended dose is 75-100 mg 4 times a day [7]. An extended release floating dipyridamole formulation may be desired to prolong the gastric residence time to enhance the solubility, improve the bioavailability and to reduce dosing frequency. Various single and multiple units of dipyridamole floating formulations has been reported in the literature, but very little work was carried in the field of multi unit mini-tablets technology.

In this study, an attempt was made to formulate and to characterize multi unit floating mini-tablets of dipyridamole to increase the bioavailability and sustain the drug release properties up to 8 h with more predictable drug release kinetics that avoids all or nothing emptying effect by employing hydrophilic polymer, HPMC K100M and hydrophobic polymer, Compritol 888 ATO.

Materials and Methods

Dipyridamole (gift samples from Dr. Reddy's laboratories, Hyderabad), Compritol ATO 888, HPMC K100M, Sodium bicarbonate, Microcrystalline cellulose, Magnesium stearate, Talc and all other ingredients are of laboratory grade.

Drug-excipient Compatibility Studies

Drug-excipient compatibility studies were performed for pure drug and physical mixture of optimized formulation of drug with polymers. The physical mixture samples were subjected to Fourier Transform infrared (FT-IR) studies. Spectra of drug and optimized formulation were taken and analyzed for any major interaction due to presence of polymers and other ingredients [7].

Micromeritic Properties [8]

The pure drug and formulation powder blend prepared were evaluated for the angle of repose, bulk density (Bd), tapped density (Td), Carr's index (CI) and Hausner's ratio (HR).Angle of repose was determined by fixed funnel method by placing ten grams of powder blend in a plugged glass funnel and was then allowed to flow through the funnel orifice by removing the cotton plug from the funnel orifice.

The height of the heap (h) formed as well as the radius of the heap (r) was noted. The angle of repose (θ) was calculated as: Tan θ = (h/r).Bd and Td of 10 g of powder blend were determined by using 50 ml graduated cylinder. The volume occupied by the blend was read and the Bd calculated in g/ml.

The cylinder containing the blend was tapped until constant volume was obtained using Bd apparatus from a height of 2 cm and the Td calculated in g/ml. The percentage compressibility (CI) was calculated from the difference between the Td and the Bd divided by the Td and the ratio expressed as a percentage. The HR is the ratio between the Td and Bd.

Determination of Lambda (ʎ) Max by Ultraviolet–visible (UV) Spectroscopy

The stock solution (1000 µg/ml) of dipyridamole was prepared in 0.1N hydrochloric acid (HCl). This solution was appropriately diluted with 0.1N HCl to obtain a concentration of 10 µg /ml. The UV spectrum was recorded in the range of 200-400 nm on double beam UV spectrophotometer. The spectrum and wavelength of maximum absorption were recorded.

Preparation of Standard Curve

The stock solution (1000µg/ml) of dipyridamole was prepared in 0.1 N HCl and

from this 20 ml of solution was taken and the volume was adjusted to 100 ml with 0.1N hydrochloric acid (200µg/ml). The above solution was suitably diluted with 0.1N hydrochloric acid to get the series of dilutions containing 2, 4, 6, 8, 10 µg/ml of dipyridamole solutions. The absorbance of these solutions were measured at 283 nm against blank i.e. 0.1 N HCl. The coefficient of correlation and equation for the line are determined.

Preparation of Dipyridamole Floating Mini Tablets

The dipyridamole floating mini matrix tablets were prepared by effervescent approach with melt granulation and direct compression techniques alone and in combination using HPMC K100M and Compritol 888 ATO at varying concentrations (20%, 30%, 40% w/w) as shown in the Table 1 along with all the excipients.

Sodium bicarbonate at concentration 10% w/w was optimized as gas generating floating agent. All the ingredients were passed through sieve 44. The formulation F1 to F3 were prepared by melt granulation method wherein Compritol 888 ATO was melted in porcelain dish on hot plate and drug was added to it. The resultant mixture was allowed to solidify at room temperature and passed through sieve 30 to form granules for compression. The formulations F4 to F6 were prepared by direct compression method using HPMC K100M. The formulations F7 to F9 were prepared by combination of Compritol 888 ATO and HPMC K100M wherein melt granulation was employed to incorporate the drug in Compritol 888 ATO polymer matrix then followed by direct compression method using HPMC K100M. The required quantities of other ingredients were added to the blend and mixed geometrically.

The blend was lubricated with magnesium stearate and talc. The final blend was compressed into mini tablets using 5 mm size round concave single tip punch on multi station rotary compression machine. In this work, each dose comprised 8 mini tablets which are equivalent to 200 mg dipyridamole.

Table 1: Composition of floating mini tablets of dipyridamole

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Dipyridamole	25	25	25	25	25	25	25	25	25
Sodium Bicarbonate	7	7	7	7	7	7	7	7	7
Compritol ATO 888	14	21	28	0	0	0	7	10.5	14
HPMC K100M	0	0	0	14	21	28	7	10.5	14
Aerosil	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Magnesium stearate	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Microcrystalline cellulose	22.6	15.6	8.6	22.6	15.6	8.6	22.6	15.6	8.6
Total weight	70	70	70	70	70	70	70	70	70

Evaluation of Physical Parameters of Floating Mini Matrix Tablets [9, 10]

Tablet Weight Uniformity

A total of 20 tablets were weighed individually, average weight was calculated and the individual tablet weights were compared with the average weight. The tablets meet the USP test if not more than two tablets are outside the percentage limit (10%) and if no tablets differs by more than two times the percentage limit.

Thickness Test

Thickness of the tablets was determined by Vernier Calipers. Three mini tablets were taken and their thickness was recorded and the average thickness along with the standard deviation is reported.

Hardness Test

Hardness of the tablet is the force applied across the diameter of the tablet to break the tablet. The hardness of 10 tablets was determined using Monsanto hardness tester and the average is calculated and reported with the standard deviation and expressed in kg/cm^2.

Friability Test

The friability of tablets was determined using Roche friabilator. Six tablets (6) were initially weighed (W_0) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again (W). The % friability was then calculated by the following equation.

$$\%F = (1-W/W_0) \times 100$$

% Friability of tablets <1% are considered as acceptable.

Drug Content

A total of 24 tablets were weighed and powdered. The quantity of powder equivalent to 200 mg of dipyridamole was dissolved in 100 ml of 0.1 N HCl. Then the solution was filtered, diluted suitably and analyzed using UV spectrophotometer at 283 nm.

In-vitro Buoyancy Studies

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

In Vitro Drug Release Studies

The *in-vitro* drug release study was performed for all the tablets using USP Type II dissolution apparatus at 50 rpm for 8 hours. Ten mini-tablets containing 200 mg of dipyridamole were placed in 900 ml 0.1 N HCl as a dissolution medium maintained at 37± 0.5℃. Aliquots of 5 ml were withdrawn at specified intervals of time, filtered and replenished with 5 ml fresh dissolution medium. Samples' absorbance was measured at λ_{max} 283 nm using UV spectrophotometer. The studies were performed in triplicate. The cumulative percentage drug released was calculated at each time interval using slope obtained from the standard curve.

Kinetic Modeling of Drug Release

The data obtained from in vitro drug release studies were fitted to the following kinetic equations:

Zero order release kinetics equation: $Qt = Q_0 + K_0t$; Where Qt is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and K_0 is the zero order release constant expressed in units of concentration/time and graph was plotted for cumulative amount of drug released vs. time. First order release kinetics equation: $\text{Log } C = \log C_0 - Kt/2.303$; where C_0 is the initial concentration of drug, K is the first order rate constant and t is the time and graph was plotted for log cumulative percentage of drug remaining vs. time.

Higuchi equation defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time and can be expressed as $Q = K_H t^{1/2}$; Where, K_H is the release rate constant. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependent.

In order to define a model, which would represent a better fit for the formulation, dissolution data were further analyzed by Peppas and Korsmeyer equation: $Mt/M\infty = K\,tn$; Where $Mt/M\infty$ is a fraction of drug released at time t, K is the release rate constant and n is the release exponent. In this model, the value of n characterizes the release mechanism of drug. For the case of cylindrical tablets, $n = 0.45$ corresponds to a Fickian diffusion mechanism, $0.45 < n < 0.89$ to non-Fickian transport, $n = 0.89$ to Case II (relaxation) transport, and $n > 0.89$ to super Case II transport.

Results and Discussion

Calibration Curve of Dipyridamole

An UV spectro-photometric method was used for estimation of dipyridamole. A solution of dipyridamole (10µg/mL) was scanned in the wavelength range of 200-400 nm and found to have maximum absorption (λ_{max}) at 283 nm. The standard plot of dipyridamole was prepared in 0.1 N HCl (pH 1.2). The standard graph showed good linearity with R^2 value of 0.9998 (Fig. 1).

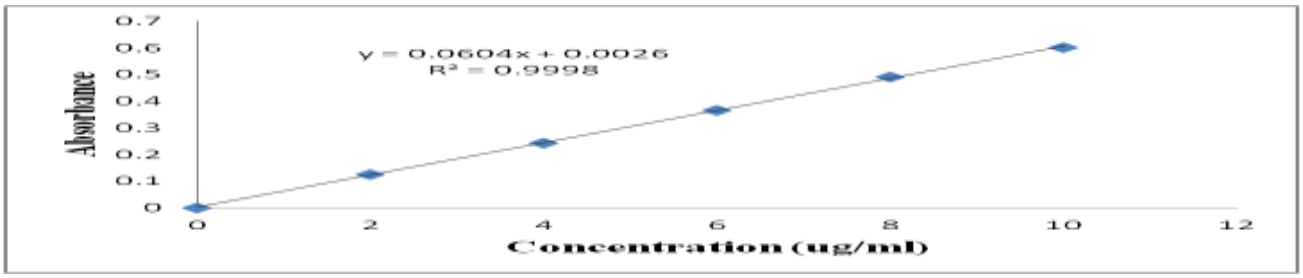

Fig.1: Standard calibration graph of dipyridamole

Drug-excipient Compatibility Studies

The FT-IR spectrum of pure drug was compared with optimized formulation. The characteristic peaks which are observed for the pure drug in the FTIR spectra (Fig. 2a) were also observed for optimized formulation (Fig. 2b) with little shifting of peaks suggesting that there is no interaction between drug and excipients (Table 2).

Table 2: Functional groups and range for dipyridamole and optimized formulation

Functional groups	Dipyridamole	Optimized formulation (F8)
O-H stretch	3443.55	3423.48
C-C stretch	2920.88	2920.64
N-H bending	1540.04	1535.99
C-C stretch	760.22	759.88

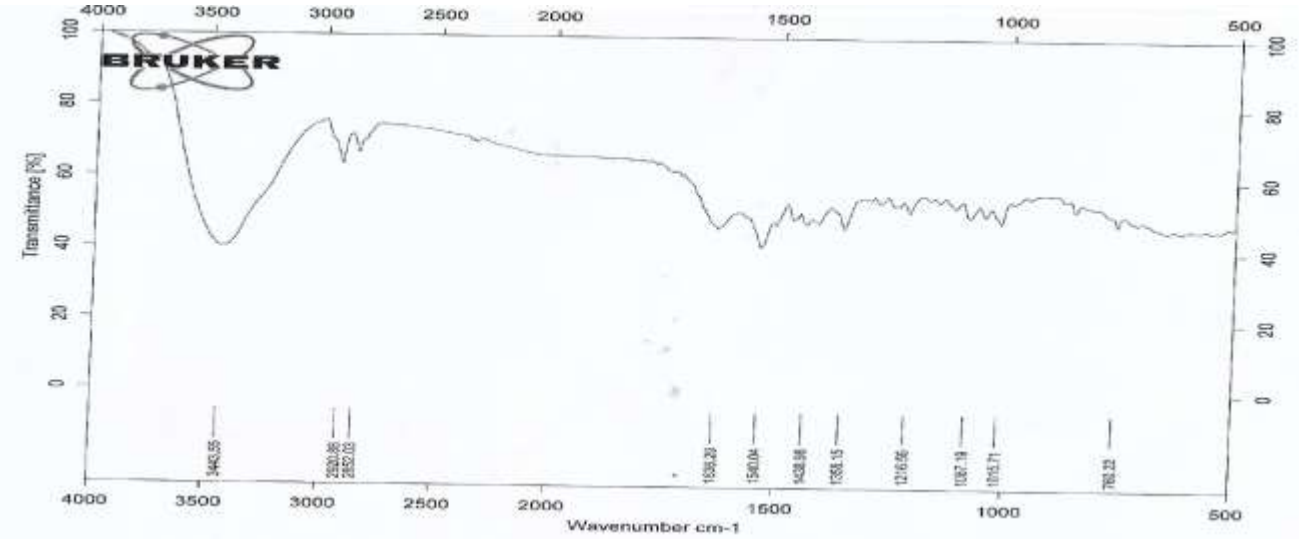

Fig. 2a: Fourier transforms infrared spectra of pure dipyridamole

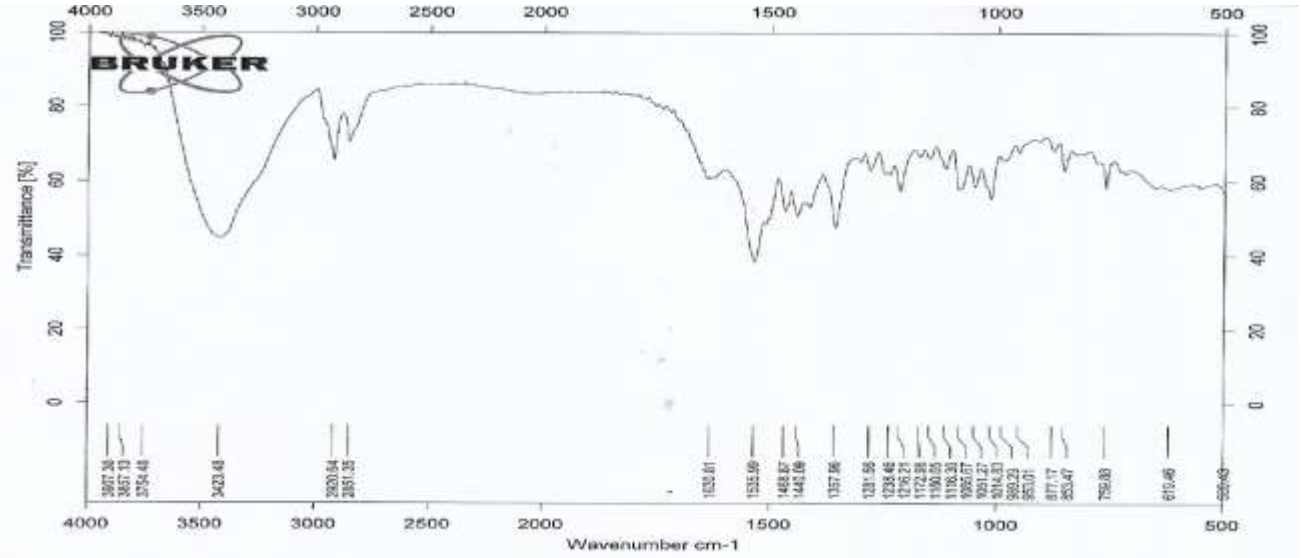

Fig. 2b: Fourier transform infrared spectra of physical mixture of dipyridamole formulation F8 blend with HPMC K100M and Compritol 888 ATO

Micromeritic Properties

The micromeritic properties of pure drug of dipyridamole showed poor flow properties as it is observed from the values of CI (28.57) and angle of repose (46.12). However, the flow properties of the formulation powder blend with diluents, glidant and lubricant showed fair to passable flow properties as it is observed from the values of CI and angle of repose. The micromeritic properties of drug and optimized bath of the formulation were shown in Table 3.

Table 3: Micromeritic properties of drug and optimized batch of dipyridamole blend

Parameters	Pure drug	F8
Angle of repose	46.12	38.21
Carr's index (%)	28.57	18.74
Hausner's ratio	1.4	1.23

Evaluation of Physical Parameters of Floating Mini Tablets

All the prepared formulations were tested for various physical parameters such as thickness, weight variation, hardness and friability. Results of the physical tests were shown in Table 4. The hardness of all the batches was found to be in the range of 4-6 Kg/cm2.

The friability of all the formulations was found to be <1%. The drug content of the formulations was in between 98% and 102%. Hence, all the dipyridamole floating mini tablets formulated by employing different concentrations of polymers and its combinations were of good quality and fulfilled the official pharmacopoeial specifications with regard to drug content, hardness and friability.

Table 4: Physical characteristics of dipyridamole floating mini tablets

Formulation code	Thickness(mm)-(n=3)	Weight Variation (n=20)	Hardness (kg/cm2) (n=10)	Friability (%) (n=6)	Assay (%) (n=3)
F1	3.64±0.02	70.22±1.14	4.26±0.10	0.15	101.23±0.96
F2	3.63±0.02	70.21±1.10	4.82±0.05	0.14	99.95±1.17
F3	3.63±0.01	69.03±1.11	4.88±0.03	0.16	100.10±0.95
F4	3.66±0.02	69.03±1.14	5.02±0.03	0.19	99.98±1.65
F5	3.64±0.03	70.11±1.12	5.32±0.03	0.17	100.12±1.04
F6	3.66±0.02	69.74±1.06	5.11±0.04	0.13	100.01±0.92
F7	3.65±0.01	70.03±1.13	4.98±0.03	0.18	98.99±1.56
F8	3.63±0.01	70.87±1.15	4.95±0.05	0.15	101.21±0.88
F9	3.64±0.02	69.75±1.01	5.02±0.03	0.16	100.12±0.21

Floating Properties of Floating Mini Matrix Tablets

All the formulations were tested for floating properties such as floating lag and total floating time. The results of the *in vitro* buoyancy study are shown in the Table 5. Sodium bicarbonate was used as a gas generating agent at 10% w/w concentration.

The sodium bicarbonate induces CO_2 generation in the presence of acidic dissolution medium (0.1 N HCl). The gas generated is trapped and protected within the gel formed by hydration of the polymer, thus decreasing the density of the tablet below 1 gm/ml, and the tablet becomes buoyant. Mini tablet formulations prepared with Compritol 888 ATO (F1 to F3) did not show floating behaviour because the formulations did not swell and hence failed to form a gel and the CO_2 generated did not get entrapped, thus these formulations failed to float the tablet.

The total floating time of other formulations (F4 to F9) was observed in between 10 to 12 h with floating lag time <2 min and showed better and desired floating characteristics. Pictorial presentation of in-vitro buoyancy study results of optimized formulation (F8) was shown in Fig. 3.

Table 5: In-vitro buoyancy data of dipyridamole floating mini tablets

Formulation code	Floating Lag Time (Seconds) (n=10)	Floating time (Hours)*
F1	NF	NF
F2	NF	NF
F3	NF	NF
F4	20±1.45	10
F5	21±1.25	>12
F6	21±2.25	>12
F7	26±3.49	10
F8	27±3.26	>12
F9	26±2.18	>12

*NF- Not Floated

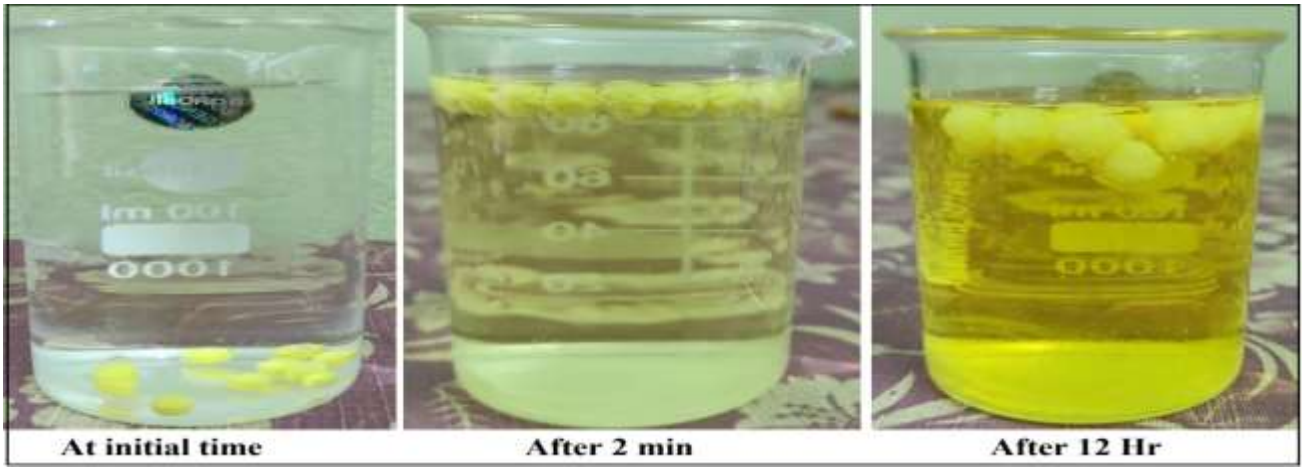

Fig. 3: Pictorial presentation of *in-vitro* buoyancy study of optimized formulation (F8)

In Vitro Drug Release Studies

The in-vitro drug release profiles of the formulations prepared with hydrophobic polymer Compritol 888 ATO are shown in Figure 4a. The drug release extended from 5-8 h and the initial 1 h drug release was varied between 17% and 38% as the polymer concentrations varies from 20-40% w/w. F1 formulation showed complete drug release within 5 h whereas formulation F2 and F3 showed 98% and 90% drug released in 7 and 8 h respectively. However, these formulations did not show any floating characteristics as the tablet formulation did not swell.

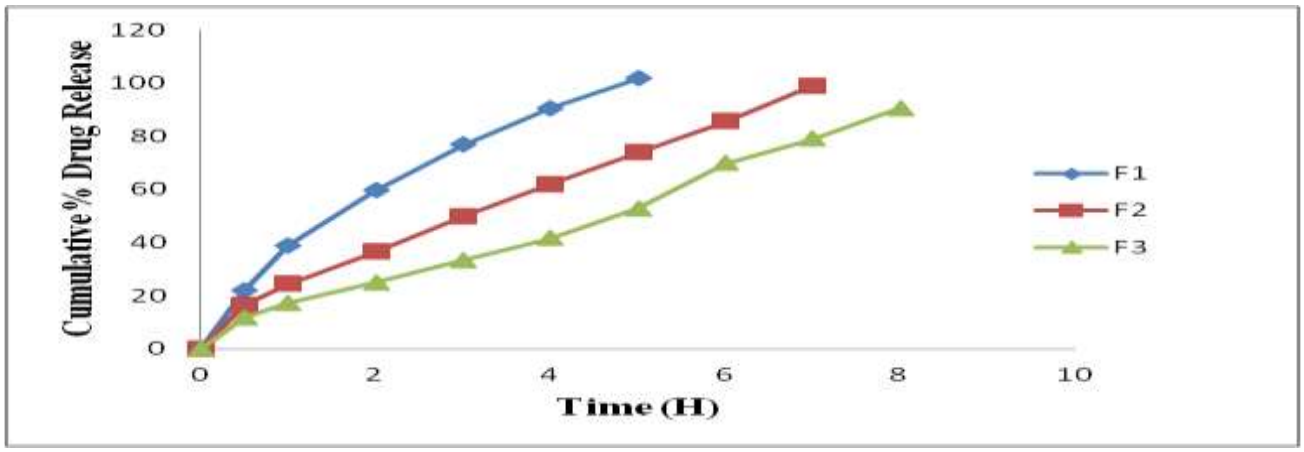

Fig. 4a: Cumulative percentage drug release of formulations with Compritol 888 ATO

The in-vitro drug release profiles of the formulations prepared with hydrophilic polymer HPMC K100M are shown in Figure 4b. The initial 1 h drug release was varied between 13-26%. F4 formulation showed complete drug release within 6 h and F5 formulation released more than 90% of drug within 7 h whereas the drug release from F6 formulation was slow and released 75% of drug at 8 h and failed to release the complete drug at 8 h.

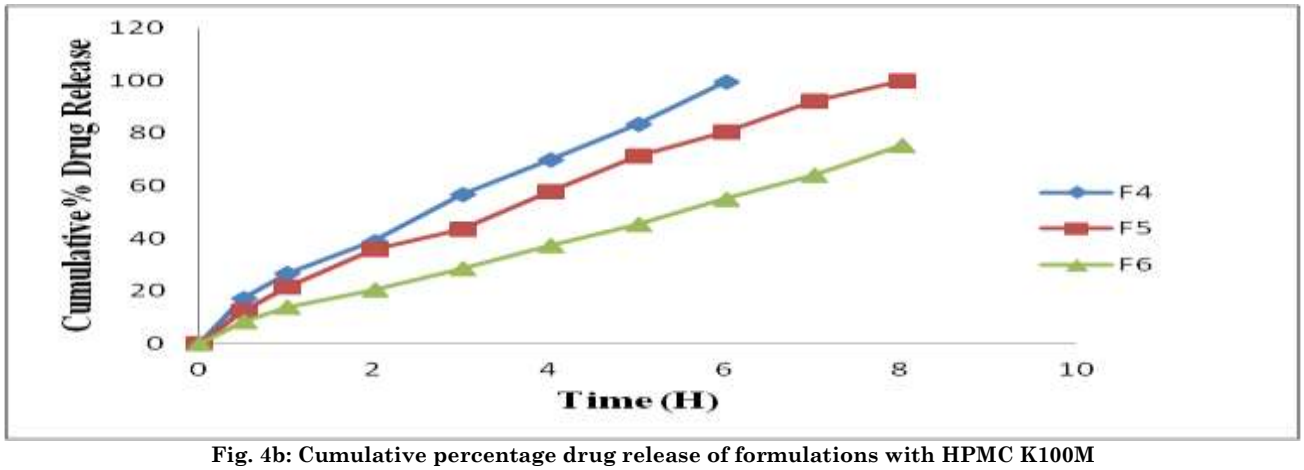

Fig. 4b: Cumulative percentage drug release of formulations with HPMC K100M

The in-vitro drug release profiles of the formulations prepared with combination of Compritol 888 ATO and HPMC K100M are shown in Figure 4c. The 1 h initial drug release was varied between 17-32%. F7 formulation showed complete drug release within 6 h. F8 formulation released almost 99% of drug at 8 h whereas the drug release from F9 formulation was slow and released only 86 % of drug in 8 h.

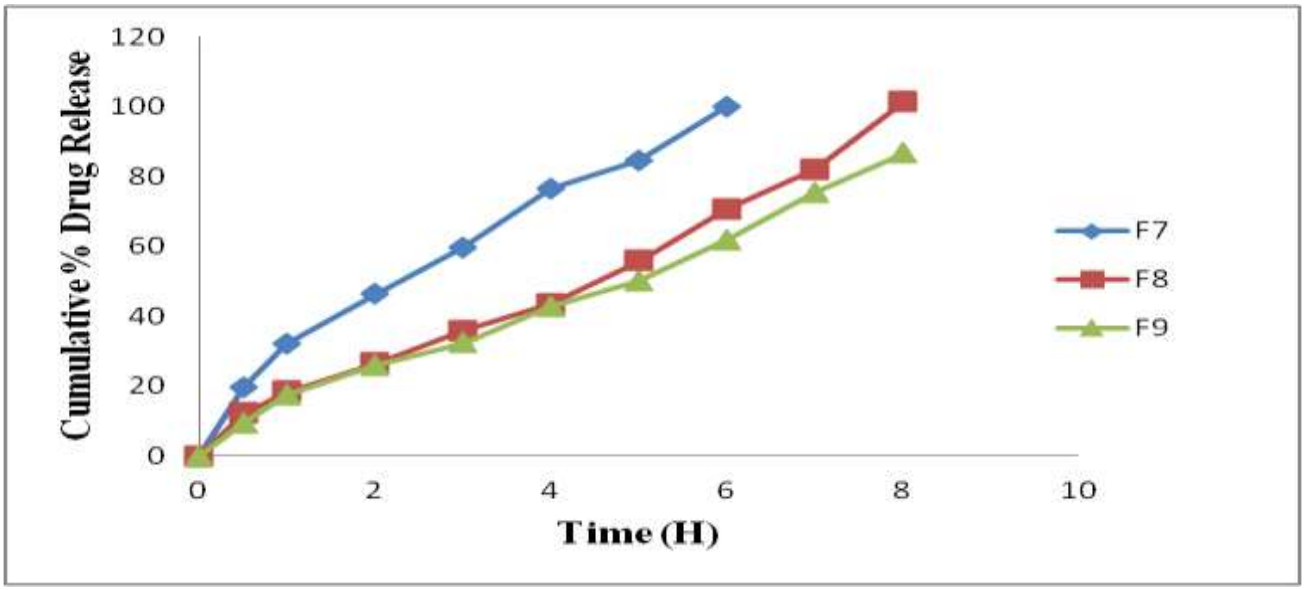

Fig. 4c: Cumulative percentage drug release of formulations with combination of Compritol 888 ATO and HPMC K100M

F8 formulation showed complete drug release within 8 h and showed better, desired drug release profile with required floating characteristics, hence it was considered as an optimized formulation. Formulations F1, F4 and F7 showed rapid drug release which may be due to insufficient polymer concentration.

Kinetic Modeling of Drug Release

Analysis of the drug release data as per zero order and first order kinetic models indicating that all the formulations followed zero order kinetics and dissolution rate constant (K) values were presented in Table 6. Higuchi plots were found to be linear with "r^2" > 0.9525 in all the dipyridamole floating mini tablets. In the analysis of release data as per Korsmeyer-Peppas equation, the release exponent "n" was in the range 0.619-0.748 indicating non-fickian diffusion as the release mechanism from all the dipyridamole floating mini tablets.

The drug release rate of dipyridamole was found to be affected by the type and concentration of the polymer used in the formulation. As the concentration of the polymer was increased, the drug release was found to be retarded.

Table 6: Regression coefficient (R^2) values of floating minitablet formulations for different kinetic models

Formulation code	Regression coefficient (R^2)				Peppas (n)	Zero order rate constant (K)
	Zero	First	Higuchi	Korsmeyer–Peppas		
F1	0.9555	0.8836	0.9901	0.9933	0.720	19.459
F2	0.9897	0.7506	0.9663	0.9950	0.632	13.224
F3	0.9906	0.8964	0.9610	0.9880	0.636	10.627
F4	0.9876	0.6939	0.9525	0.9612	0.619	15.549
F5	0.9892	0.7130	0.9662	0.9954	0.722	12.181
F6	0.9963	0.9509	0.9323	0.9926	0.748	8.8735
F7	0.9728	0.6450	0.9826	0.9953	0.610	15.424
F8	0.9861	0.6601	0.9572	0.9903	0.638	11.49
F9	0.9870	0.8272	0.9760	0.9921	0.715	10.404

Conclusion

In this research work, an attempt has been made to develop multi unit floating mini-tablets of dipyridamole by effervescent approach using the polymers HPMC K100M and Compritol 888 ATO to sustain the drug release properties up to 8 h with more predictable drug release kinetics that avoids all or nothing emptying effect in order to improve bioavailability and patient compliance. According to the above results, optimised floating mini-tablet formulation

(F8) prepared by employing combination of 15% w/w HPMC K100M and 15% w/w Compritol 888 ATO with 10% w/w sodium bicarbonate offered better desired in-vitro floating time and drug dissolution profile and the adopted method yielded uniform and reproducible floating mini matrix tablets. Thus all the major objectives of this investigation were fulfilled.

References

1. Swarbrick J (2007) Encyclopedia of Pharmaceutical Technology. 3rd ed. Vol 2. New York: In form a Healthcare, 1082-103.
2. Kawashima Y, Takeuchi H, Yamamoto H (2000) Handbook of Pharmaceutical Controlled Release Technology. New York: Marcell Dekker Inc., 505-25.
3. Meka L, Kesavan B, Kalamata VN, Eaga CM, Bandari S, Vobalaboina V, Yamsani MR (2009) Design and evaluation of polymeric coated minitablets as multiple unit gastroretentive floating drug delivery systems for furosemide, J. Pharm. Sci., 98: 2122-2132
4. Ishak RAH, Awad GAS, Mortada ND, Nour SAK (2007) Preparation, in vitro and in vivo evaluation of stomach-specific metronidazole-loaded alginate beads as local anti-Helicobacter pylori therapy. J. Control Release, 119: 207-214.
5. Priyanka, Kumar K, Teotia D (2018) A comprehensive review on pharmaceutical mini tablets, Journal of Drug Delivery and Therapeutics, 8(6):382-390.
6. Kim HH, Liao JK (2008) Translational therapeutics of dipyridamole. Arteriosclerosis, thrombosis, and vascular biology, 28(3): s39-s42.
7. Birajdar Shivprasad M, Darveshwar Jagdeep (2012) Development and evaluation of floating-mucoadhesive dipyridamole tablet. Asian Journal of Pharmaceutical Research and Health Care, 4:78-89.
8. Lachman L, Lieberman HA, Kanig JL (1987) The Theory and Practice of Industrial Pharmacy. 3rd ed. Bombay: Varghese Publication House, 171-96.
9. Sally A, El-Zahaby, Abeer A. Kassem, Amal H El-Kamel (2014) Design and evaluation of gastroretentive levofloxacin floating mini-tablets-in-capsule system for eradication of Helicobacter pylori. Saudi Pharmaceutical Journal, 22: 570-579.
10. Panwar Mangal S (2015) Development and characterization of sustain release gastro retentive floating microsphere of diltiazem hydrochloride for the treatment of hypertension. Asian Journal of Pharmaceutics, 9 (02):107-112

