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PREFORMULATION, FORMULATION DEVELOPMENT AND DRUG RELEASE STUDIES OF DIPYRIDAMOLE FLOATING MICROBALLOONS

Seelam Ramya Krishna *, A. Ramu and S. Vidyadhara

Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur - 522510, Andhra Pradesh, India.

Keywords:

Dipyridamole, Preformulation, Gastric transit time, Gastric emptying, Emulsion solvent evaporation

Correspondence to Author:
Seelam Ramya Krishna

Research Scholar,
Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur - 522510, Andhra Pradesh, India.

E-mail:ramya.krishna.seelam@gmail.com

ABSTRACT: For the drugs possessing stomach and upper intestine as the absorption window, it has become high practical importance to improve their gastric residence time. The in vitro performance of the drug delivery being highly variable is ascertaining as gastric emptying is one of the complex mechanisms. Intense researches are being carried out for the development of multiparticulate systems, which are of greater importance than the single unit dosage forms in oral drug delivery. Floating microballoons offer more reproducible drug absorption, reduce the risk of local irritation, and improve the bioavailability of the drug. In the current research work, Dipyridamole, a BCS class – II drug was formulated as controlled release microballoons using ethyl cellulose as polymer and span 80 as the surfactant to improve the gastric retention of the drug. Preformulation studies *viz.* solubility, partition coefficient, micromeritics, and the drug excipient compatibility studies using Fourier transform infrared spectrophotometer and Differential Scanning Calorimeter were carried out. The emulsion solvent evaporation method was employed to develop controlled release dipyridamole floating microballoons. Different formulations of floating microballoons were formulated by considering five process and formulation factors *viz.* surfactant concentration, volume of solvent, volume of internal phase, polymer concentration, and rotational speed. All the formulations were subjected to *in-vitro* drug release studies, and the lowest and highest release rate was found to be 0.096 hr^{-1} and 0.251 hr^{-1} in the formulations F34 and F15, respectively. The Peppas n values of all the formulations were above 0.5, indicating the drug release mechanism was non-fickian diffusion.

INTRODUCTION: Dipyridamole is an anti-platelet drug known chemically as methyl 2-({6-[bis(2- hydroxyethyl) amino]- 4, 8-bis(piperidin-1-yl)-[1, 3]diazino[5, 4-d]pyrimidin-2-yl}(2-hydroxy-ethyl) amino) ethan-1-ol. It has a chemical formula ($C_{24}H_{40}N_8O_4$) and a molecular weight of 504.6256 g/mol. It helps to keep blood flowing by stopping platelets from clumping together and by keeping heart blood vessels open.

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Dipyridamole (DIP) is a platelet inhibitor. Clinically it is used as an antithrombotic agent. DIP has a short biological half-life of 2-3 h [1, 2]. Oral dosage forms of DIP exhibit variable absorption with limited bioavailability ranging from 11-44 %. DIP exhibits a pH-dependent solubility with good solubility at low pH (37°, 36.5 g/l at pH 1.0) and poor solubility at a higher pH (37°, 0.02 g/l at pH 7.0) [3].

The major absorption sites of DIP are stomach and duodenum [1-3]. Due to short biological half-life of 2 to 3 h, DIP should be frequently administered or as a controlled release dosage form. Dipyridamole appears to act *in-vivo* by synergistically modifying several biochemical pathways, including a)

inhibition of platelet cAMP-phosphodiesterase; b) potentiation of adenosine inhibition of platelet function by blocking reuptake by vascular and blood cells, and subsequent degradation of adenosine; and possibly, c) potentiation of PGI_2 anti-aggregatory activity and enhancement of PGI_2 biosynthesis. These independent processes inhibit platelet function by increasing platelet cAMP through both a reduction in enzymatic cAMP-degradation and stimulation of cAMP formation *via* activation of adenyl cyclase by adenosine and possibly PGI_2. Only the inhibition of cAMP phosphodiesterase appears to be involved in the dipyridamole inhibition of isolated platelets *in-vitro*, since adenosine and PGI_2originate *in-vivo* from tissues other than platelets and any blood concentrations existing *in-vivo* will disappear before platelet-rich plasma has been prepared for in vitro platelet studies.

Preformulation [4-6] commences when a newly synthesized drug shows sufficient pharmacologic promise in animal models to warrants evaluation in man. These studies should focus on those physico-chemical properties of the new compound that could affect drug performance and the development of an efficacious dosage form. A thorough understanding of these properties may ultimately provide a rationale for formulation design, or support the need for molecular modification.

The aim of this study was to determine some of the physicochemical properties such as solubility, pKa, dissolution, melting point, assay development, stability in Solution, stability in solid-state, microscopy, bulk density, flow properties, and excipient compatibility.

Hence, formulating the Dipyridamole into microballoons helps in increasing gastric retention [7, 8] times, thereby maintaining constant plasma concentration. In the current research work, Dipyridamole was formulated as floating microballoons by emulsion solvent evaporation technique to improve its gastric residence time thereby enhancing its bioavailability.

In the current research work, one of the major quality characteristics of controlled release multiparticulate systems *i.e.* drug release profile and the release kinetics were studied.

MATERIALS: Dipyridamole drug was received as a gift sample from Mankind Pharma, Hyderabad. Ethylcellulose, span 80, methanol, diethyl ether, and liquid paraffin were purchased from SD Fine Chemicals Ltd, Mumbai.

Preformulation Studies:

Construction of Calibration Curve: 50 mg of Dipyridamole was dissolved in 50 mL of 0.1N HCl buffer placed in a 50 mL of volumetric flask (stock solution). From this stock solution, 10mL was taken and made upto 100ml using 0.1N HCL, to attain the working standard 100 µg/ml. From that, a series of dilutions were made to get 3, 6, 9, 12, 15µg/ml concentrations. The absorbance was measured using a double beam UV-visible spectro-photometer (Thermo Scientific) at wavelength maxima of 283nm. From the obtained absorbance values, a standard calibration curve was constructed.

Physical and Physicochemical Properties of Dipyridamole:

Solubility Determination: Shake flask method was utilized for determining the solubility of Dipyridamole. In this method, the drug was added to 10mL of 0.1M HCL and shaken at a predetermined time. Excess amount of Dipyridamole was added to a saturation level till the observation of the presence of undissolved drug. Orbital shaker was used to shake the flask for 24 h. After a specified time, the slurry was filtered, and the filtrate was collected for analysis. After suitable dilutions, the sample was analyzed using a UV-Visible spectrophotometer at the maximum wavelength of 283nm.

Partition Coefficient Determination: Shake flask method[9] was used to determine the partition coefficient of Dipyridamole. 1gm of the drug was dissolved in a mixture of 10mL chloroform and 10mL water, both phases were then mixed together in a separating funnel and shaken for 1hr and was allowed to stand long enough for the phases to separate and the solute concentration was measured in each solvent after suitable dilutions by using UV-Visible spectrophotometer at the maximum wavelength of 283nm.

Melting Point Determination: The melting point of Dipyridamole was determined by using the

Capillary method. A capillary tube that was sealed initially at one open end was filled with Dipyridamole drug sample. By repeated pounding of the capillary tube against, the powder was pushed to the bottom of the tube. About 2.0mm to 3.0mm of sample height was maintained for optimum results and reproducibility. Then the capillary tube was kept in the melting point apparatus, and the temperature at which the drug was melted was noted.

Micrometric Properties: The micromeritics[10] properties such as particle size, angle of repose, compressibility index, and Hausner's ratio were characterized for Dipyridamole.

Bulk Density: Into a 10mL measuring cylinder, 5gms of accurately weighed drug (Dipyridamole) was placed. Without disturbing the cylinder, the volume occupied by the drug was noted and the bulk density was calculated using the below equation (values expressed in gm/cm^3).

Bulk Density = Weight of sample / Volume of sample

Tapped Density: Into a 10mL measuring cylinder, 5gms of a drug (Dipyridamole) was placed. At an interval of 2 seconds, the cylinder was dropped onto a hard wooden surface from a height of one inch for 100 times. The final volume was recorded, and the tapped density was calculated by the following equation (values expressed in gm/cm^3)

Tapped Density = Weight of sample / Tapped Volume of sample

Carr's Index (%): The Carr's index is an indication of the compressibility of a powder. Carr's index is determined as the flow property of the blend depends on the carr's index. A Carr's index greater than 25% is considered to be an indication of poor flowability and below 15% of good flowability. It is calculated by the formula.

Carr's Index (%) = Tapped density-Bulk density / Tapped density × 100

Angle of Repose (θ): The angle of repose is indicative of the flowability of the substance. The funnel was adjusted in such a way that the stem of the funnel lies 2.5 cm above the horizontal surface. The sample powder was allowed to flow from the funnel, so the height of the pile just touches the tip of the funnel. The diameter of the pile was determined by drawing a boundary along the circumference of the pile and taking the average of three diameters. The angle of repose is calculated by using this formula:

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} h/r$$

Where θ is angle of repose, h is the height of the pile, r is the radius of the pile.

Hausner's Ratio: The Hausner's ratio is an indication of the compressibility of a powder and the flowability of the powder. A Hausner's ratio greater than 1.25 is considered to be an indication of poor flowability. The observations for the flow properties determinations are recorded. It is calculated by the formula:

Hausner's ratio = Tapped density / Bulk density × 100

Drug-Excipient Compatibility Studies:

FT-IR Spectroscopy: The physicochemical compatibility between Dipyridamole and ethylcellulose used in the research was carried out by subjecting to Fourier transform infrared spectrophotometer, Bruker. KBR pellet method was used to carry the physicochemical compatibility studies [10]. The samples were prepared by mixing 100 mg of drug with 100mg of ethylcellulose used in the preparation of floating microballoons. These samples were scanned under diffuse reflectance mold, and spectra were recorded in the wave number region between 4000 cm^{-1} to 400 cm^{-1}. The spectra obtained for the pure drug was compared with that of the physical mixtures of the drug with a polymer.

Differential Scanning Calorimetry Study: The physical incompatibilities of the drug and excipients can be evaluated quickly by Differential Scanning Calorimeter (DSC) as it changes in the appearance, the shift of melting endotherms and exotherms, and/or variations in the corresponding enthalpies of reaction. The DSC thermograms of pure drug and other excipients were recorded. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10 °C/min over a temperature range of 50 °C to 300 °C.

Preparation of Floating Microballoons: [7, 11] Liquid paraffin was taken in a beaker, and 0.0% or

0.25% or 0.5% v/v of span 80 was added to it to get the oily phase. The oil phase was placed under the mechanical stirrer and set 400/550/700 rpm. In another beaker, the polymer is dissolved in a mixture of methanol and diethyl ether, to which drug was added and dissolved by placing on a vertex mixture for 2 min to get the organic phase. The organic phase was added drop by drop to the oil phase under stirring. Hollow microspheres were obtained by stirring continuously 4-5 h until the organic solvents were evaporated completely. To remove the traces of liquid paraffin, the obtained hollow microspheres were washed with petroleum ether and then dried. The compositions of various formulations were shown in **Table 1**.

TABLE 1: FORMULATION CODES OF DIPYRIDAMOLE BISULPHATE MICROBALLOONS

Standard order	Formulation code	Factor A	Factor B	Factor C	Factor D	Factor E
1	F1	50.00	20.00	7.50	0.25	550.00
2	F2	75.00	20.00	7.50	0.25	550.00
3	F3	50.00	60.00	7.50	0.25	550.00
4	F4	75.00	60.00	7.50	0.25	550.00
5	F5	62.50	40.00	5.00	0.00	550.00
6	F6	62.50	40.00	10.00	0.00	550.00
7	F7	62.50	40.00	5.00	0.50	550.00
8	F8	62.50	40.00	10.00	0.50	550.00
9	F9	62.50	20.00	7.50	0.25	400.00
10	F10	62.50	60.00	7.50	0.25	400.00
11	F11	62.50	20.00	7.50	0.25	700.00
12	F12	62.50	60.00	7.50	0.25	700.00
13	F13	50.00	40.00	5.00	0.25	550.00
14	F14	75.00	40.00	5.00	0.25	550.00
15	F15	50.00	40.00	10.00	0.25	550.00
16	F16	75.00	40.00	10.00	0.25	550.00
17	F17	62.50	40.00	7.50	0.00	400.00
18	F18	62.50	40.00	7.50	0.50	400.00
19	F19	62.50	40.00	7.50	0.00	700.00
20	F20	62.50	40.00	7.50	0.50	700.00
21	F21	62.50	20.00	5.00	0.25	550.00
22	F22	62.50	60.00	5.00	0.25	550.00
23	F23	62.50	20.00	10.00	0.25	550.00
24	F24	62.50	60.00	10.00	0.25	550.00
25	F25	50.00	40.00	7.50	0.00	550.00
26	F26	75.00	40.00	7.50	0.00	550.00
27	F27	50.00	40.00	7.50	0.50	550.00
28	F28	75.00	40.00	7.50	0.50	550.00
29	F29	62.50	40.00	5.00	0.25	400.00
30	F30	62.50	40.00	10.00	0.25	400.00
31	F31	62.50	40.00	5.00	0.25	700.00
32	F32	62.50	40.00	10.00	0.25	700.00
33	F33	50.00	40.00	7.50	0.25	400.00
34	F34	75.00	40.00	7.50	0.25	400.00
35	F35	50.00	40.00	7.50	0.25	700.00
36	F36	75.00	40.00	7.50	0.25	700.00
37	F37	62.50	20.00	7.50	0.00	550.00
38	F38	62.50	60.00	7.50	0.00	550.00
39	F39	62.50	20.00	7.50	0.50	550.00
40	F40	62.50	60.00	7.50	0.50	550.00
41	F41	62.50	40.00	7.50	0.25	550.00

Characterization of Microballoons:

Drug Release Studies: [12] USP II Dissolution test apparatus was used to perform the in-vitro dissolution studies for all the floating micro-balloons using 900mL of 0.1N HCl as the dissolution medium. The apparatus was set at 100 rpm, and the sample was withdrawn for every 30 min for the first 2 h and thereafter for every 1 h upto 12 h. After necessarily suitable dilutions, the samples were analyzed by using a UV-Visible spectrophotometer at the maximum wavelength of 283nm.

Drug Release Kinetic Studies: [13] The data obtained from *in-vitro* release studies were fitted to various kinetic equations to find out the mechanism of drug release. The kinetic models used are:

$$Qt = K_0 t \text{ (zero-order equation)}$$

$$\ln Q_t = \ln Q_0 - K_1 t \text{ (first-order equation)}$$
$$Q_t = K_h t_{1/2} \text{ (Higuchi equation)}$$

Where Q_t is the amount of drug release in time t, Q_0 is the initial amount of drug in the microballoons and K_0, K_1, and Kh are rate constants of zero order, first order, and Higuchi equations respectively. Further to confirm the mechanism of drug release, the first 60% of drug release was fitted in the Korsemeyer-Peppas model.

$$M_t / M_\infty = k\, t^n$$

where M_t is the amount of drug release at time t and M_∞ is the amount release at time t=∞; thus M_t / M_∞ is the fraction of drug released at time t, k is the kinetic constant, and n is the diffusion exponent which can be used to characterize both mechanisms for both solvent penetration and drug release.

RESULTS AND DISCUSSION:

Preformulation Studies:

Construction of Calibration Curve: The calibration of Dipyridamole was carried out by using a double beam UV spectrophotometer (Thermo Scientific) in 0.1N HCL. The absorbances were measured at λ max of 288nm shown in **Table 2**. The linear co-efficient was found to be closer to 1 (*i.e.* 0.999) at a concentration range between 3-15µg/mL. The regression equation generated was y=0.055x as shown in **Fig. 1**.

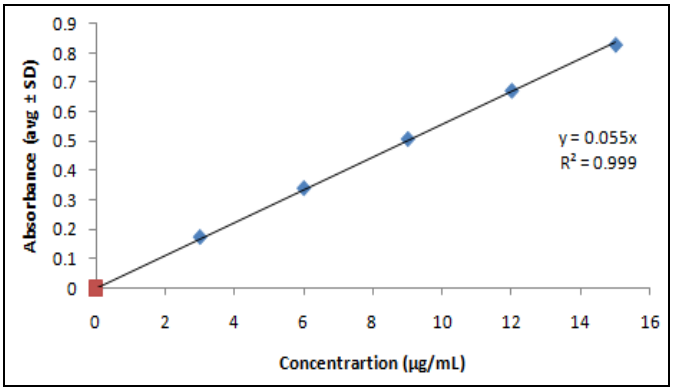

FIG. 1: CALIBRATION CURVE FOR DIPYRIDAMOLE

TABLE 2: CALIBRATION CURVE DATA FOR DIPYRIDAMOLE

S. no.	Conc. (µg/mL)	Absorbance (avg ± SD)
1	3	0.176±0.016
2	6	0.342±0.026
3	9	0.509±0.042
4	12	0.673±0.055
5	15	0.829±0.079

Physical and physicochemical properties of Dipyridamole: In the preformulation studies, the physical and physicochemical properties of Dipyridamole were determined for solubility, melting point, partition coefficient, and micromeritics and the results were shown in **Table 3** which were all correlated with literature values.

TABLE 3: PHYSICAL AND PHYSICOCHEMICAL PROPERTIES OF DIPYRIDAMOLE

S. no.	Parameter		Observed Result (Avg ± SD)
1	Solubility (mg/ml)	Water	0.0066 ± 0.0006
		0.1N Hydrochloric acid	36.73 ± 0.00034
		Acetate buffer pH 3.4	1.384 ± 0.12
		Phosphate buffer pH 5.8	0.013 ± 0.0012
		0.1N Sodium hydroxide	0.0045 ± 0.00045
2	Flow properties	Bulk density	0.276 ± 0.026
		Tapped density (g/ml)	0.423 ± 0.041
		Hausner's ratio	1.53 ± 0.95
		Carr's Index (%)	34.751 ± 2.95
		Angle of repose (ɵ)	27.915 ± 1.98
3	Melting point (^{0}C)		163 ± 15.55
4	Partition coefficient		3.955 ± 0.112

Drug-Excipient Compatibility Studies:

FT-IR Spectroscopy: Compatibility studies of drug and polymer were conducted by employing I.R spectral studies. IR spectra of pure Dipyridamole and the physical mixtures of drugs and polymers were shown in **Fig. 2, 3,** and **4,** respectively. As shown in **Table 4**, the characteristic peaks of the Dipyridamole were observed with the spectra of Dipyridamole and the physical mixtures. It was inferred from the FT-IR results that no interaction existed between the drug and polymers as the identical principle peaks were observed in all the cases.

TABLE 4: FT-IR DRUG EXCIPIENT COMPATIBILITY STUDIES

S. no.	Peak feature	Wavelength (cm^{-1})		
		Dipyridamole	Dipyridamole + ethyl cellulose	Dipyridamole + Span80
1	O-H Inplane blend of primary alcohol	1251	1251.20	1249.23
2	C-O stretch of primary alcohol	1051	1052.18	1054
3	C-N stretch of 3° amine	1150, 1173	1150.96	1173.24
4	C-N stretch of aromatic secondary amino group	1282, 1303	1282.19, 1303.39	1281.72, 1302.31
5	C-N stretch of aromatic 3° amino group	1358	1358.38	1358.17

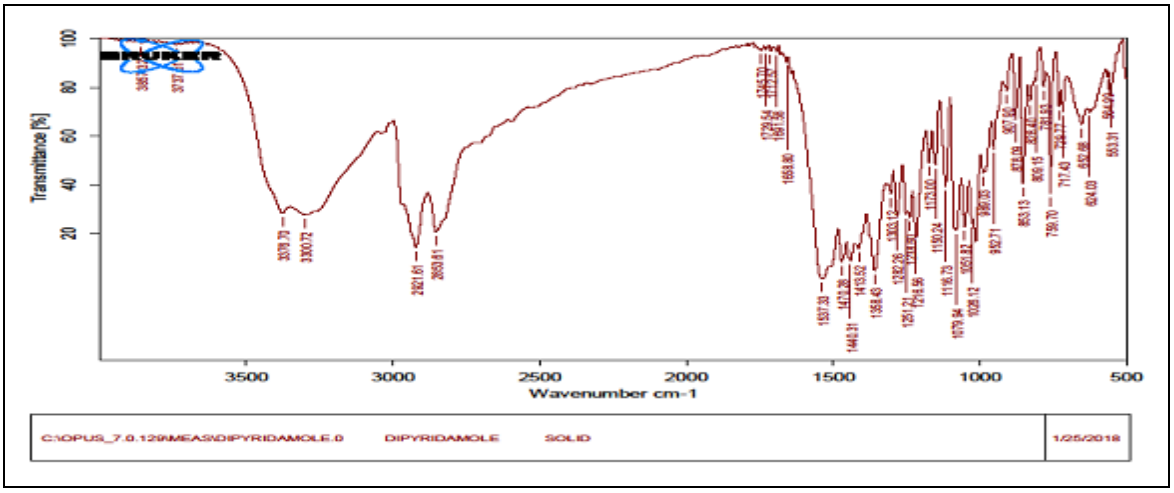

FIG. 2: FT-IR SPECTRA OF DIPYRIDAMOLE

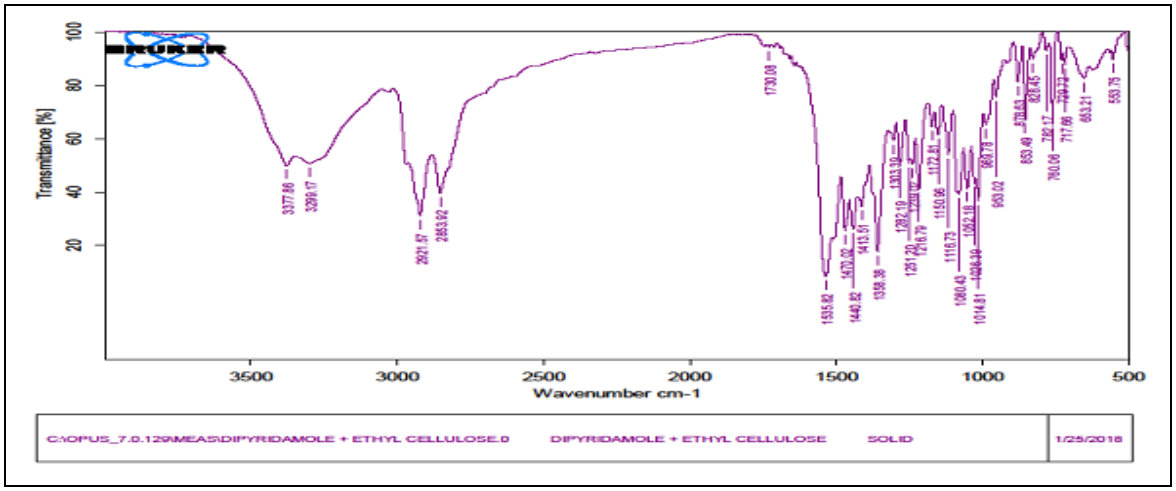

FIG 3: FT-IR SPECTRA OF DIPYRIDAMOLE AND ETHYL CELLULOSE PHYSICAL MIXTURE

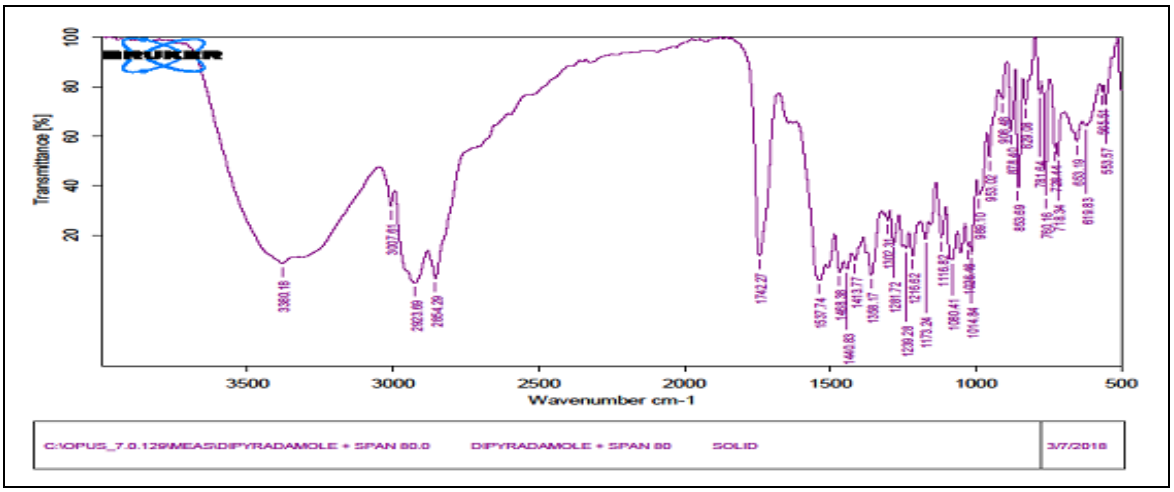

FIG. 4: FT-IR SPECTRA OF DIPYRIDAMOLE AND SPAN 80 PHYSICAL MIXTURE

DSC Studies: In the current work, DSC has been used to study the physical and chemical interaction between the drug and the excipients used. Drug excipient interactions play a vital role with respect to the release of drug from the formulation amongst others. It was observed in the DSC graphs that there was no chemical interaction [13] between dipyridamole and the polymer used as there wasn't any difference in the melting point of dipyridamole which was found to be 163.1 °C for dipyridamole alone and 161.2 °C for dipyridamole when mixed with ethyl cellulose as shown in **Fig. 5** and **Fig. 6,** respectively.

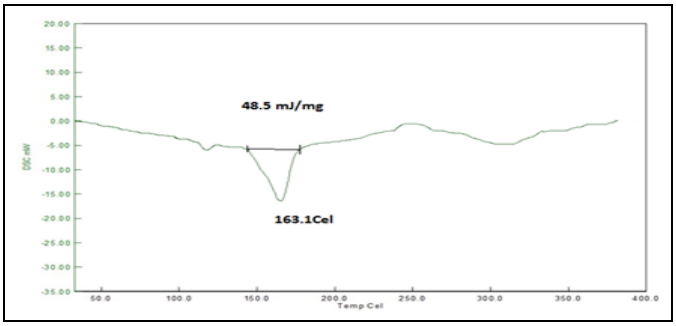

FIG 5: DSC SPECTRUM OF PURE DIPYRIDAMOLE

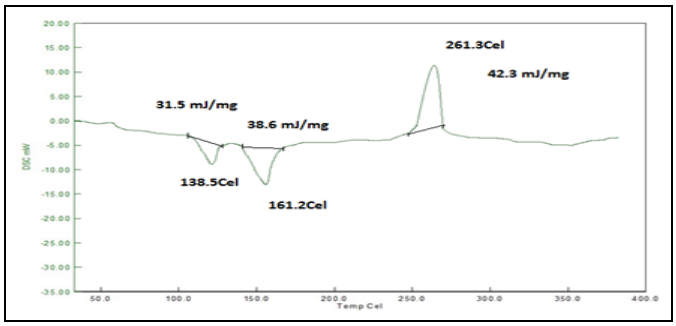

FIG. 6: DSC SPECTRUM OF PHYSICAL MIXTURE OF DIPYRIDAMOLE AND ETHYL CELLULOSE

Characterization of Microballoons: Drug Release Studies:

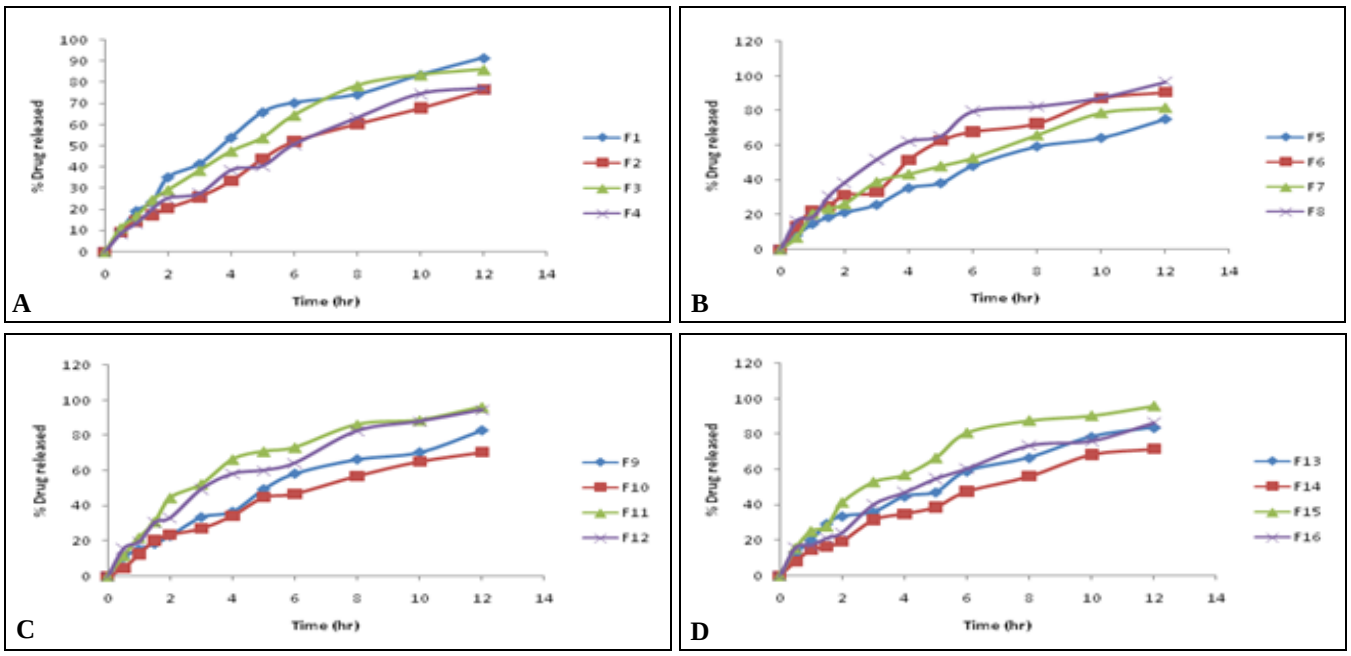

FIG. 7: DRUG RELEASE PROFILES OF (A) F1 TO F4; (B) F5 TO F8; (C) F9 TO F12 AND (D) F13 TO F16

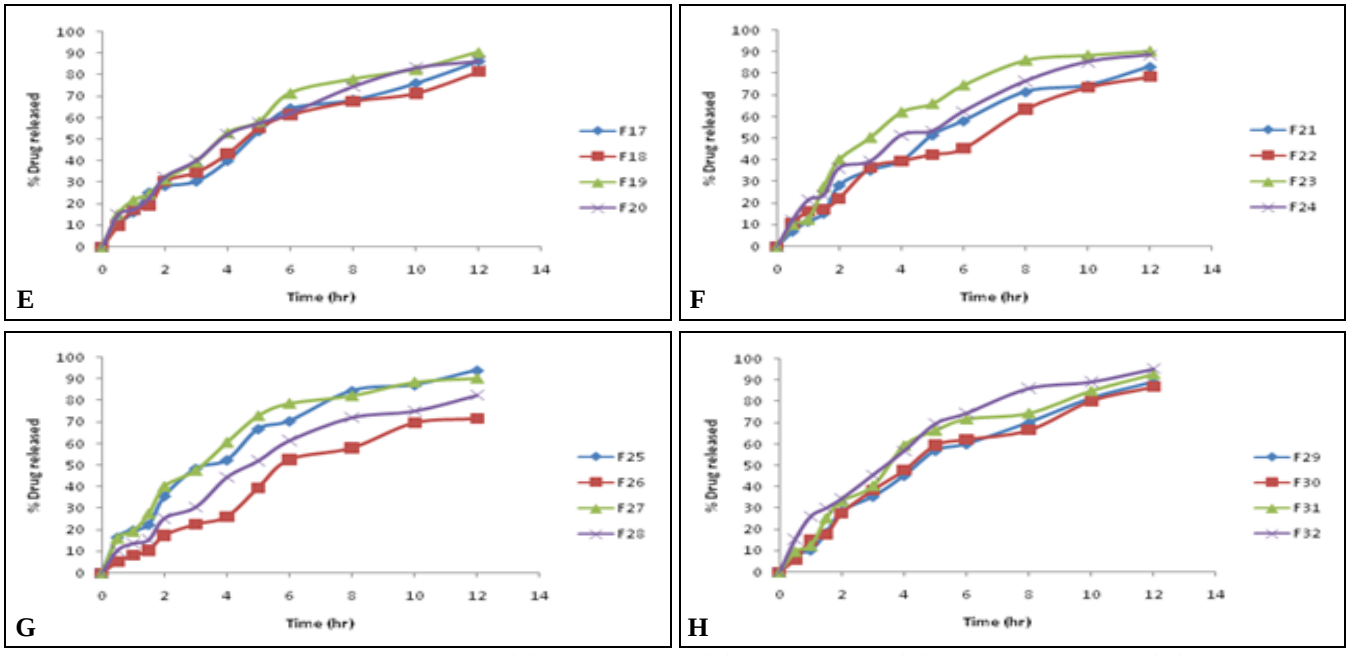

FIG. 8: DRUG RELEASE PROFILES OF (E) F17 TO F20; (F) F21 TO F24; (G) F25 TO F28 AND (H) F29 TO F32

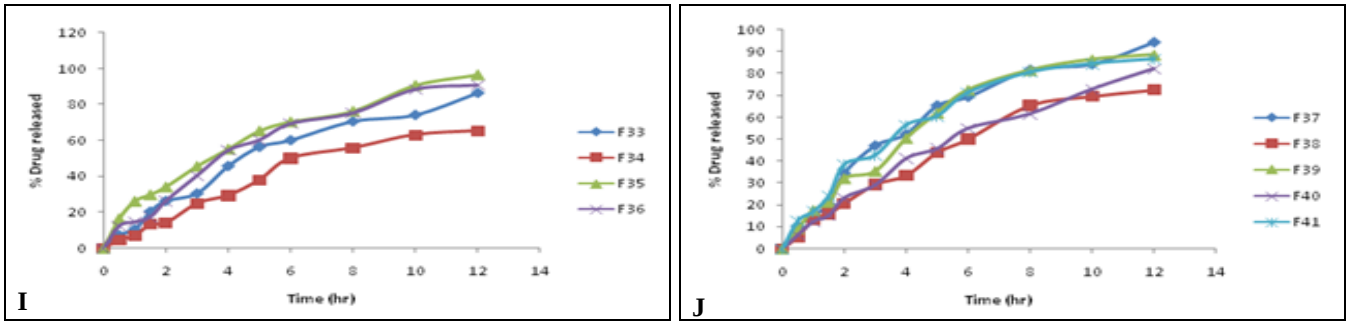

FIG. 9: DRUG RELEASE PROFILES OF (I) F33 TO F36 AND (J) F37 TO F41

All the formulated dipyridamole microballoons were subjected to in-vitro drug release studies, and the drug release was found to be controlled to a maximum in case of F34 with a release rate constant of 0.096 hr^{-1} and F15 showed rapid drug release at a rate of 0.251 hr^{-1}. The drug release profiles of F1 to F16, F17 to F32, and F33 to F41 were represented in **Fig. 7, 8,** and **9,** respectively.

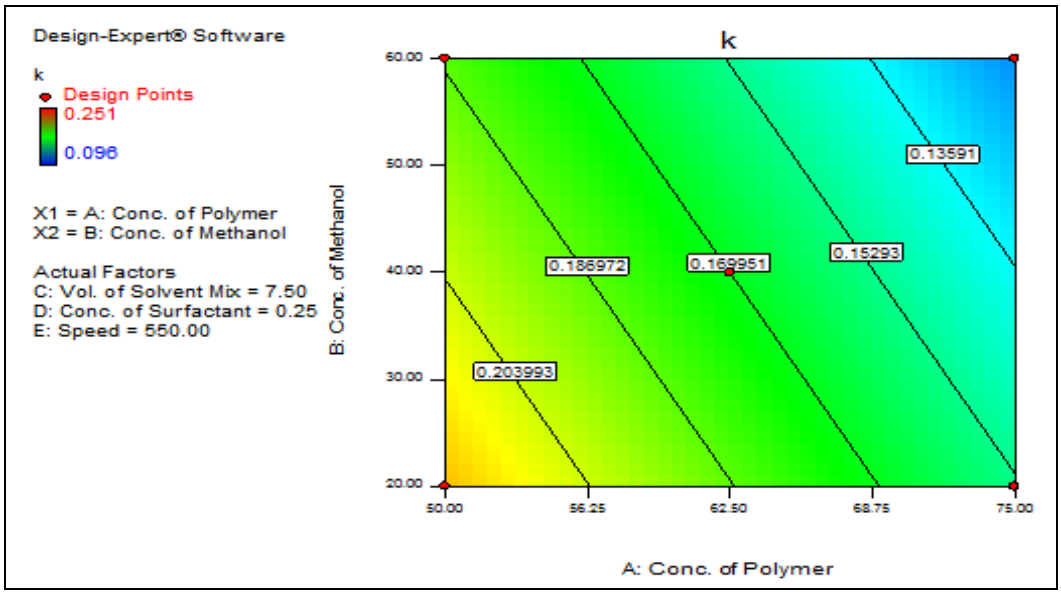

FIG. 10: EFFECT OF POLYMER CONCENTRATION AND METHANOL CONCENTRATION ON RELEASE RATE CONSTANT

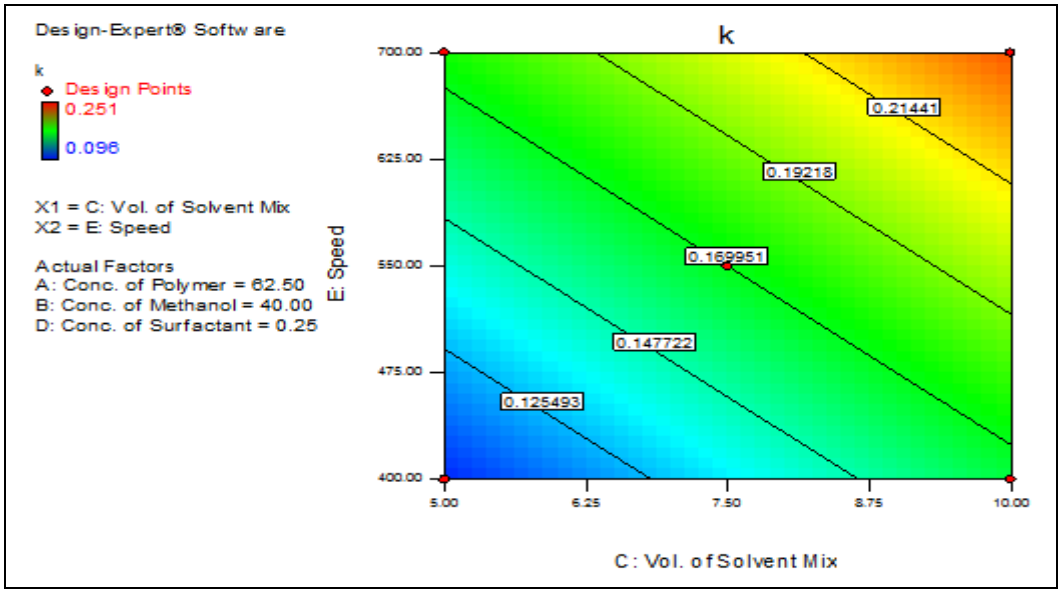

FIG. 11: EFFECT OF INTERNAL PHASE VOLUME AND SPEED OF ROTATION ON RELEASE RATE CONSTANT

TABLE 5: ANOVA FOR DRUG RELEASE RATE OF THE DIPYRIDAMOLE MICROBALLOONS

Response	Source	SS	Df	MSS	F – value	p – value	Inference
Release rate constant	Model	0.059	5	0.012	20.98	< 0.0001	Significant
	A	0.018	1	0.018	31.78	< 0.0001	Significant
	B	$4.935x10^{-3}$	1	$4.935x10^{-3}$	8.73	0.0056	Significant
	C	0.015	1	0.015	26.12	<0.0001	Significant
	D	$5.290x10^{-4}$	1	$5.290x10^{-4}$	0.94	0.3399	Not Significant
	E	0.021	1	0.021	37.34	<0.0001	Significant
	Residual	0.020	35	$5.651x10^{-4}$			

From **Fig. 10** it was inferred that upon an increase in the polymer concentration, the drug release rate was found to be decreased. This might be attributed to the increased path length at high polymer concentrations for the diffusion of an entrapped drug, which leads to a decrease in the drug release rate [7]. Upon an increase in the concentration of methanol in the internal phase, the drug release rate was found to be decreased. At a high concentration of methanol, the slow evaporation rate results in the controlled formation of microballoons with a tight surface and thus might have lead to a decrease in drug release rate.

Fig. 11 illustrates that upon an increase in the volume of the internal phase, there was an increase in the drug release rate. Due to the less viscosity of the dispersed phase, the high internal phase volumes resulted in microballoons with a smaller size. As more surface area comes in contact with dissolution medium in the smaller particles, there was an increase in the drug release rate [7]. The drug release rate was found to be decreased with the increase in the speed of rotation. The high speed of rotation resulted in microspheres with smaller size. Small size particles have more surface area, so the contact with the dissolution medium was more, which lead to an increase in drug release rate.

It was inferred from **Table 5** that there was no effect of surfactant on the drug release rate as the p-value found to be 0.3399 which is more than the probable p-value (>0.100) indicating that the effect of Factor D on the drug release rate was not significant

Drug Release Kinetic Studies: The data of the drug release kinetics of all Dipyridamole micro-balloon formulations were represented in **Table 6,** and it was inferred that all the formulations were found to have followed first-order kinetics of drug release. The exponent (n value) form Peppas plots of all the formulations were found to be above 0.5, thus indicating all the formulations followed non-Fickian diffusion [14] as their drug release mechanism.

TABLE 6: DRUG RELEASE KINETICS OF DIPYRIDAMOLE MICROBALLOONS

S. no.	Formulation	Regression values			Peppas 'n' value	Drug release rate constant (k hr^{-1})
		Zero-order	First-order	Higuchi		
1	F1	0.796	0.985	0.97	0.687	0.193
2	F2	0.923	0.994	0.944	0.685	0.117
3	F3	0.855	0.989	0.967	0.675	0.173
4	F4	0.921	0.987	0.948	0.700	0.125
5	F5	0.927	0.989	0.95	0.682	0.110
6	F6	0.830	0.982	0.968	0.621	0.190
7	F7	0.863	0.985	0.971	0.704	0.142
8	F8	0.717	0.963	0.975	0.905	0.242
9	F9	0.902	0.984	0.953	0.68	0.136
10	F10	0.894	0.990	0.958	0.793	0.105
11	F11	0.682	0.979	0.971	0.659	0.248
12	F12	0.781	0.978	0.984	0.599	0.218
13	F13	0.805	0.983	0.985	0.576	0.149
14	F14	0.916	0.990	0.953	0.691	0.108
15	F15	0.713	0.987	0.977	0.592	0.251
16	F16	0.844	0.988	0.97	0.609	0.159
17	F17	0.874	0.981	0.958	0.667	0.155
18	F18	0.829	0.982	0.968	0.674	0.141
19	F19	0.802	0.990	0.977	0.599	0.189

20	F20	0.815	0.995	0.979	0.617	0.171
21	F21	0.904	0.992	0.941	0.81	0.145
22	F22	0.904	0.983	0.952	0.654	0.126
23	F23	0.736	0.979	0.951	0.741	0.216
24	F24	0.823	0.989	0.98	0.621	0.181
25	F25	0.818	0.988	0.972	0.616	0.221
26	F26	0.957	0.978	0.881	0.892	0.108
27	F27	0.683	0.972	0.962	0.608	0.215
28	F28	0.892	0.991	0.942	0.726	0.147
29	F29	0.911	0.984	0.945	0.807	0.169
30	F30	0.872	0.987	0.95	0.814	0.161
31	F31	0.808	0.979	0.953	0.754	0.203
32	F32	0.751	0.990	0.982	0.5888	0.238
33	F33	0.894	0.942	0.983	0.805	0.153
34	F34	0.935	0.905	0.981	0.894	0.096
35	F35	0.774	0.991	0.948	0.561	0.235
36	F36	0.867	0.947	0.986	0.722	0.196
37	F37	0.828	0.975	0.959	0.739	0.213
38	F38	0.920	0.985	0.936	0.795	0.116
39	F39	0.843	0.986	0.949	0.737	0.193
40	F40	0.937	0.989	0.938	0.804	0.133
41	F41	0.756	0.979	0.968	0.652	0.186

CONCLUSION: In an aim to develop floating microballoons, dipyridamole was studied extensively for its preformulation parameters. Five different formulation and process variables *viz*. polymer concentration, surfactant concentration, the volume of internal phase, the concentration of methanol in the internal phase, and speed of rotation was considered for the formulation of dipyridamole floating microballoons. In the current research work, the emulsion solvent evaporation technique was employed to formulate floating microballoons as 41 formulations. All the formulations were subjected to drug release and release kinetic studies effectively, and the results were suitably analyzed.

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REFERENCES:

1. Offman E, Schobelock MJ, Brickl R, VanderMaelen CP, Ehrlich J and Eisert W: Pharmacokinetics and pharmacodynamics of the antiplatelet combination aspirin (acetylsalicylic acid) plus extended-release dipyridamole are not altered by coadministration with the potent CYP2C19 inhibitor omeprazole. American Journal of Cardiovascular Drugs: Drugs, Devices and other Inventions. 2013; 13: 113-20.
2. Eisert WG: Platelets. Academic Press, London, Edition 3, 2013: 1155-70.
3. Khalil A, Belal F, Abdullah A and Al-Badr: Profiles of Drug Substances, Excipients and Related Methodology, Academic Press, London, Edition 1, Vol. 31, 2005: 215-80.
4. Fiese EF and Hagen TA: The Theory and Practice of Industrial Pharmacy, CBS Publishers & Distributers, New Delhi, Special Indian Edition, 2009: 171-96.
5. Sinko PJ: Martin's Physical pharmacy and Pharmaceutical Sciences. Lippincott Williams and Wilkins, 6th 2011.
6. Begum FU, Farheen M, Kauser A, Haseena A, Sultana S, Afreen Z and Anjum Z: Design and evaluation of regioselective drug delivery system by using dipyridamole deug as model. IOSR Journal of Pharmacy and Biological Sciences 2017; 12: 1-7.
7. Srikar G, Shanthi D, Ramesh J, Kalyani V and Nagamma I: Floating microspheres: A prevailing trend in the development of gastroretentive drug delivery system. Asian Journal of Pharmaceutics 2018; 12: 235-42.
8. Kumar R, Kamboj S, Chandra A, Gautam PK and Sharma VK: Microballoons: An advance avenue for gastroretentive drug delivery system- A review. UK Journal of Pharmaceutical and Biosciences 2016; 4: 29-40.
9. Andres A, Roses M, Rafols C, Bosch E, Espinosa S, Segarra V and Huerta JM: Setup and validation of shake-flask procedures for the determination of partition coefficients (logD) from low drug amounts. European Journal of Pharmaceutical Sciences 2015; 76: 181-91.
10. Srikar G, Avula P, Annapurna S and Boola M: Development of extended release matrix tablets of felodipine through solid dispersions for better drug release profile by a 32 factorial design. Indian Journal of Pharmaceutical Education and Research 2016; 50: S89-S99.
11. Mishra A, Rathore S, Marothia D and Chauhan CS: Formulation and evaluation of floating microspheres of an

anti-diabetic agent. International Journal of Drug Development & Research. 2018; 10: 38-42.
12. Galatage ST, Killedar SG, Patil A, Alman AA and Harale S: Development and characterization of micropaticles of Sumatriptan succinate carrier system via nasal route. International Journal of Pharmaceutical Sciences & Research 2019; 10(9): 4194-4200.
13. Srikar G and Rani AP: Study on infuence of polymer and surfactant on *in-vitro* performance of biodegradable aqueous-core nanocapsules of tenofovir disoproxil fumarate by response surface methodology. Brazilian Journal of Pharmaceutical Sciences 2019; 55: e18736.
14. Raghuveer P, Rani AP, Desavatu M, Chaitanya AS and Srikar G: Formulation of monodisperse alginate (micro) spheres containing tenofovir for extended release dosage form. Research Journal of Pharmacy and Technology 2017; 10: 1070-76.

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