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Original Article

STUDY OF INFLUENCE OF FORMULATION AND PROCESS VARIABLES ON ENTRAPMENT EFFICIENCY AND PARTICLE SIZE OF FLOATING MICRO BALLOONS OF DIPYRIDAMOLE BY DOE

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ABSTRACT

Objective: In the current research work, dipyridamole, a BCS class–II drug, was aimed to be formulated as floating controlled release microballoons using ethyl cellulose as polymer and span 80 as surfactant to improve the gastric retention of drug as the multi-particulate dosage forms have tremendous advantages over single unit dosage forms.

Methods: Microballoons were prepared by the emulsion solvent evaporation method. Prepared microballoons were characterized for entrapment efficiency, particle size, floating behavior and drug release studies. The study of effect of various formulation and process parameters like surfactant concentration, solvent volume, the volume of internal phase, polymer concentration, rotation speed on the drug entrapment efficiency and particle size of the microballoons were carried by using Box–Benhken to optimize the formulated microballoons.

Results: The smallest particle size of the microballoons was found to be 205.9 µm in the F32 formulation. The highest drug entrapment efficiency was found to be 93.4% in the F34 formulation. Buoyancy studies showed all the formulations have good floating characteristics that lasted for a minimum of 24 h. The maximum yield of microballoons was found in the F7 formulation with 91.8% yield. The final results were statistically treated using ANOVA and were found to be significant (p value<0.05).

Conclusion: Thus, the obtained results and their statistical interpretations indicated floating microballoons of dipyridamole were formulated effectively.

Keywords: Optimization, Gastric emptying, Dipyridamole, Gastric transit time, Box–Benhken design, Microballoons

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INTRODUCTION

Oral controlled release dosage forms have the potential to upkeep an effective concentration in the system for a longer duration. It provides ease in dosage administration to the patient but the benefits are yet obstructed due to the short gastric retention time (GRT) and the unpredictable rapid gastric rate may cause partial drug release in the absorption zone of the patient's body hence, hampering the efficiency of the dosage. It has caused awaited development in oral gastroretentive drug delivery systems (GRDDS) [1].

Multi-particulate dosage form is one such approach so as to improve the bioavailability of the drug. A method to improve the gastric residence time is to incorporate the drug into a floating device that is less dense than the gastric fluid [2]. Uniform distribution of the multi particulate dosage in the gastric content could result in more reproducible absorption and a reduced risk of local irritation than single-unit dosage forms. Such prolonged gastric retention not only controls the time but also the space in the stomach by maintaining the delivery system positioned at a steady site and thereby properly delivering the drug.

Dipyridamole is a phosphodiesterase inhibitor that blocks uptake and metabolism of adenosine by erythrocytes and vascular endothelial cells. Dipyridamole also potentiates the anti-aggregating action of prostacyclin. Dipyridamole, a non-nitrate coronary vasodilator that also inhibits platelet aggregation, is combined with other anticoagulant drugs, such as warfarin, to prevent thrombosis in patients with valvular or vascular disorders. Dipyridamole is also used in myocardial perfusion imaging, as an antiplatelet agent, and in combination with aspirin for stroke prophylaxis. Dipyridamole likely inhibits both adenosine deaminase and phosphodiesterase, preventing the degradation of cAMP, an inhibitor of platelet function. It belongs to BCS class–II drugs with low solubility and high permeability. Hence a controlled release formulation of dipyridamole helps in improving its bioavailability [3-7]. Hence formulating the dipyridamole into microballoons helps in increasing the gastric retention time, thereby maintaining constant plasma concentration. In the current research work, dipyridamole was formulated as floating microballoons to improve its gastric residence time, thereby enhancing its bioavailability.

MATERIALS AND METHODS

Materials

Dipyridamole pure 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.

Methods

Preparation of floating microballoons

Experimental design

In the current research work, micro balloons were prepared by the emulsion solvent evaporation method. The optimization of the influence of various formulation and process variables (independent variables) on the responses of microballoons was carried out by using the response surface model. The independent variables considered in this study were the polymer concentration, concentration of methanol in the internal phase, volume of the internal phase, concentration of surfactant in the external phase and speed of rotation. The responses opted were entrapment efficiency and particle size of microballoons. All the five variables were taken at three levels each and so the Box-Behnken design was selected and performed by employing Stat-Ease Design Expert software.

Method of preparation of floating microballoons

The drug was added to the polymer which was dissolved in the mixture of methanol and diethyl ether and thereafter placed on the vertex mixture for 2 min to get the organic phase. Liquid paraffin was taken in another 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 constant stirring on a mechanical stirrer at an rpm of 400/550/700 to which the organic phase was added drop by drop. The stirring was continued for 4-5 h until the organic solvents were evaporated completely to yield hollow microspheres. The obtained hollow microspheres were washed with petroleum ether to remove paraffin and then dried. The compositions of various formulations were shown in table 1 where Factor A represents the polymer concentration in the total weight of microspheres; Factor B represents the concentration of methanol in the internal phase, Factor C indicates the total volume of the internal phase, Factor D indicates the concentration of Span 80 (surfactant) and Factor E represents the speed in rpm [8-10].

Characterization of microballoons

Determination of percentage yield of microballoons

Prepared microballoons were collected and weighed. The weight of microballoons was divided by the total weight of all the nonvolatile components that were used in the preparation of the microballoons and multiplied by 100, which gives the % yield of microballoons. Percentage yield of floating micro balloons is represented by following formula.

$$\% \text{ yield} = \frac{\text{Actual weight of product}}{\text{Total weight of drug and excipients}} \times 100$$

Table 1: Formulation codes with combinations of various factors according to Box–Behnken design

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

Drug entrapment efficiency and loading efficiency

To determine loading efficiency, microballoons were taken, thoroughly triturated and 100 mg drug equivalent microballoons were placed in 100 ml beaker containing 50 ml of 0.1N HCL. The beaker was subjected to constant stirring on a magnetic stirrer at 100 rpm. After 3 h, the sample was withdrawn and the absorbance was measured at 283 nm against 0.1N HCL as blank by thermo UV spectrophotometer. Percentage of drug entrapment and the percentage loading efficiency were calculated as following:

$$\text{DEE} = \frac{\text{Amount of drug actually present}}{\text{Amount of drug taken}} \times 100$$

$$\text{LoadingEfficiency}(\%) = \frac{\text{Amount of drug actually present}}{\text{Theoretical amount of drug + polymer}} \times 100$$

Floating characterization

From each formulation, 100 microballoons were taken in a 100 ml beaker containing 70 ml of water and allowed to stand for about 24

h. After 24 h, the number of microballoons floating on the surface was observed [11-15].

$$\% \text{ Buoyancy} = \frac{\text{No. of floated microballoons after 24h}}{\text{No. of floating microballoons taken}} \times 100$$

Particle size and surface morphology

The particle size analysis of all the formulations was carried by optical microscopy. The formulation with the highest drug entrapment efficiency was subjected to surface morphology analysis using scanning electron microscope [16].

Drug release studies

F7, F21and F34 microballoons with high entrapment efficiency were subjected to *in vitro* dissolution studies in USP II paddle-type dissolution test apparatus using 900 ml of 0.1N HCl as the dissolution medium and the rpm was maintained at 100. The samples were withdrawn at 30 min, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 h and the samples were analyzed by using a UV-Visible spectrophotometer at the maximum wavelength of 283 nm after suitable dilutions [17].

Drug release kinetic studies

The mechanism of drug release from the micro balloons was studied from the data obtained from *in vitro* release studies, which were fitted to various kinetic equations. The kinetic models used are:

$Qt = K_0 t$ (zero-order equation)

$\ln Q_t = \ln Q_0 - K_1 t$ (first-order equation)

$Q_t = K_h t_{1/2}$ (Higuchi equation)

Where Q_t is the amount of drug release in time t, Q_0 is the initial amount of drug in the microsphere, 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 Korsmeyer-Peppas model.

$$M_t/M_\infty = k\, tn$$

where M_t is the amount of drug release at time t and M_∞ is the amount release at time $t=\infty$; 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 of solvent penetration and drug release.

Experimental design validation and ANOVA

The optimization of the formulation and process parameters which influence different characteristics of microballoons can be achieved effectively only by the application of different statistical techniques. The various experimental designs that can be applied to the optimization of the parameters include empirical models, factorial designs [18], fractional factorial designs, simplex optimization, and response surface methodology [19]. All the combinations of factors were taken in a single block with one center point per block to attain a total of 41 runs as given by the Box-Behnken design of the response surface method [20]. Linear model of ANOVA was performed to identify whether the selected factors were significant or not individually and also together [21].

Table 2: Results of some physical characterization studies of floating microspheres

S. No.	Formulation	Entrapment efficiency (%)	Loading efficiency (%)	Particle size (µm)	Buoyancy (%)	Yield (%)
1	F1	83.7±3.4	41.85±1.7	266.2±7.6	90.33±2.3	88.3±1.2
2	F2	92.4±1.6	23.1±0.4	210.3±4.9	88.67±1.7	86.3±2.3
3	F3	78.3±2.8	39.15±1.4	281.5±5.3	91.33±3.3	84.2±1.8
4	F4	88.7±1.9	22.18±0.5	453.2±10.2	86.00±2.7	84.5±1.5
5	F5	81.5±5.1	30.56±1.9	468.1±6.4	89.00±2.1	89.7±1.4
6	F6	77.1±4.2	28.91±1.6	362.5±7.1	94.67±1.7	81.4±3.1
7	F7	92.8±2.5	34.8±0.9	353.6±8.2	93.67±3.0	91.8±3.5
8	F8	75.2±1.9	28.2±0.7	216.8±6.0	91.67±2.4	82.3±2.8
9	F9	91.5±2.4	34.31±0.9	471.1±9.2	93.33±3.7	79.9±1.7
10	F10	89.3±3.1	33.48±1.2	422.8±8.7	94.00±1.8	84.6±1.9
11	F11	82.7±2.2	31.01±0.8	244.3±8.1	96.00±2.6	81.1±2.4
12	F12	78.6±4.1	29.47±1.5	315.6±3.4	91.33±3.3	91.5±1.1
13	F13	83.3±1.7	41.35±0.8	345.4±7.2	89.67±2.8	88.2±2.8
14	F14	92.4±3.2	23.1±0.8	455.8±8.0	86.33±1.9	76.4±3.2
15	F15	77.5±5.4	38.75±2.7	231.5±6.4	88.33±1.5	82.4±4.2
16	F16	80.2±6.3	20.05±1.6	329.6±8.9	94.33±1.3	86.3±1.6
17	F17	85.1±2.1	31.91±0.8	452.1±9.2	87.67±1.7	79.6±2.2
18	F18	92.3±1.7	34.61±0.6	391.5±5.9	89.67±2.7	78.8±2.7
19	F19	78.9±3.5	29.58±1.3	322.4±4.9	92.00±2.3	84.1±1.6
20	F20	85.7±3.8	32.13±1.4	211.6±3.7	85.00±3.1	91.2±2.8
21	F21	94.1±3.9	35.28±1.5	409.2±5.6	91.00±3.0	77.9±2.4
22	F22	91.1±4.5	34.16±1.7	402.0±6.9	95.33±2.6	84.7±2.5
23	F23	84.5±4.1	31.68±1.5	299.5±3.8	94.00±2.4	86.5±1.6
24	F24	83.1±6.2	31.16±2.3	307.2±4.7	90.67±4.1	84.4±1.9
25	F25	76.8±4.3	38.4±2.1	331.3±5.1	88.33±2.7	79.1±2.2
26	F26	85.8±5.7	21.45±1.4	486.5±8.4	87.67±4.3	78.1±2.7
27	F27	78.4±5.2	39.2±2.6	219.9±8.9	93.33±3.9	86.7±2.3
28	F28	91.5±4.4	22.88±1.1	432.1±3.7	93.00±4.3	85.5±3.1
29	F29	92.4±3.2	34.65±1.2	593.2±6.2	89.33±3.7	82.4±3.0
30	F30	78.1±3.1	29.28±1.2	342.2±6.3	88.67±2.3	82.6±1.6
31	F31	77.6±2.4	29.1±0.9	345.6±4.4	96.67±1.7	86.8±1.9
32	F32	73.8±2.6	27.67±1.0	205.9±5.0	95.67±1.9	91.2±2.1
33	F33	86.1±1.9	43.05±1.0	362.4±7.8	91.33±2.5	87.3±3.2
34	F34	93.4±1.8	23.35±0.4	628.6±8.4	92.33±2.7	81.1±3.1
35	F35	74.2±2.4	37.1±1.2	215.7±5.7	87.00±3.1	78.5±2.9
36	F36	84.7±3.1	21.18±0.8	358.2±8.2	93.33±2.0	79.8±1.9
37	F37	86.4±2.9	32.4±1.1	395.3±9.6	93.67±2.2	83.9±2.4
38	F38	84.8±2.7	31.8±1.0	449.8±4.6	91.00±3.7	89.7±1.6
39	F39	90.6±4.1	33.97±1.5	294.7±5.8	85.00±4.1	79.2±1.3
40	F40	88.1±4.3	33.03±1.6	332.2±7.3	89.67±4.4	87.4±2.1
41	F41	81.2±1.8	30.45±0.7	342.6±7.9	91.33±3.1	89.1±2.5

All the results are expressed as Average±standard deviation for n =3.

RESULTS AND DISCUSSION

Determination of percentage yield of microballoons

The results of the percentage yield of dipyridamole microballoons were showed in table 2. All the formulations of microballoons were prepared by the solvent evaporation technique and from the results, more than 76.4% yield was observed in any case, which indicated that the solvent evaporation technique, along with the selected experimental conditions was highly effective for the preparation of floating microspheres.

Drug entrapment efficiency and Percentage loading efficiency

The drug entrapment efficiency of all the formulations was found to be above 73.8%, inferring a considerably better entrapment of the drug in the polymer matrix occurred as shown in table 2. The maximum drug entrapment efficiency was found to be in the formulations F7, F21 and F34, having drug entrapment efficiency above 92.8%. The percent loading efficiency of the drug in different formulated microballoons was shown in table 2 and the loading efficiency for all the microballoons were found to be within a range of 21% to 44%.

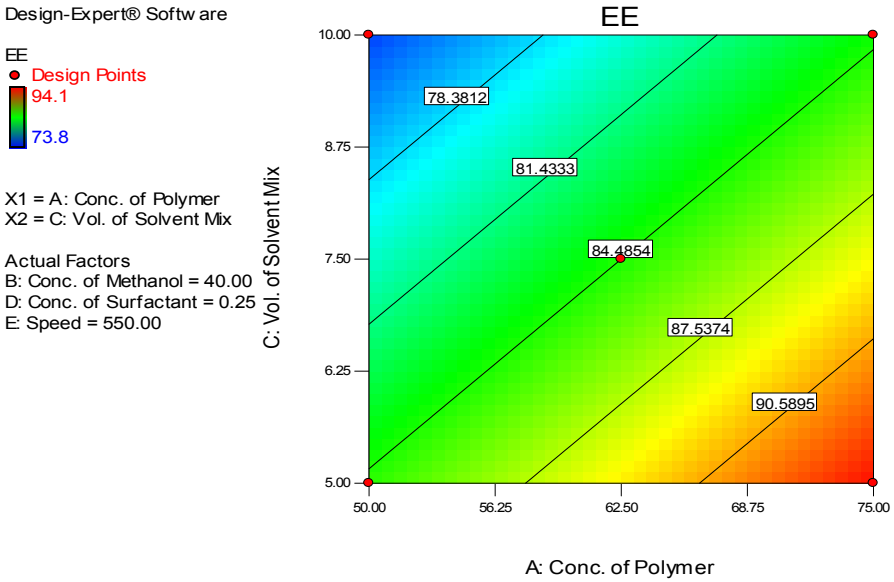

Fig. 1: Contour plot of effect of polymer concentration and volume of internal phase on entrapment efficiency

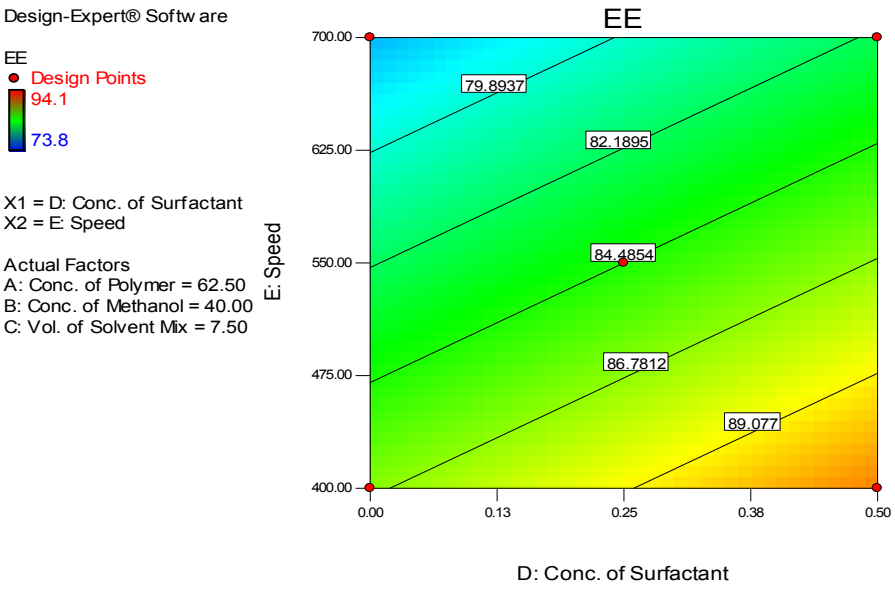

Fig. 2: Contour plot of effect of surfactant concentration and speed on entrapment efficiency

The influence of different formulation and process parameters on the drug entrapment efficiency was plotted as contour plots using Design Expert software shown in fig. 1 and 2. It was depicted from fig. 1 that the drug entrapment efficiency was found to increase with the increase in the concentration of polymer which might be attributed to the stronger polymer matrix at higher amounts of

polymer, which might hold the drug tightly and hinder the leakage of the drug, thus finally resulting in increased entrapment efficiency. The results obtained were correlated with those reported by Krishnamachari Y *et al.* [22]. Upon an increase in the concentration of methanol in the internal phase, the rate of evaporation might be decreased because of the higher melting point of methanol than that of diethyl ether. During slow evaporation for longer time, more amount of drug might be diffused out of the microspheres thus resulted in decreased entrapment efficiency.

Fig. 2 infers that the drug entrapment efficiency of the microballoons increased as the concentration of the surfactant was increased, which might be due to the fact that as the surfactant concentration increases, the stability of the emulsion increases, which helps in the deposition of polymer efficiently on the globule thereby increasing the drug entrapment efficiency. This effect of surfactant on entrapment efficiency was correlated with that reported by Dinarvand R *et al.* [23] and Rojas J *et al.* [24]. As the speed of rotation of the mixing was increased, the entrapment efficiency decreased because at high rpm; there might be rapid solvent evaporation, which might lead to more amount of drug out of the globules along with the solvent. The drug entrapment efficiency results data of the dipyridamole microballoons obtained from the experimental data were statistically treated using analysis of variance and it was inferred from table 3 that the hypothetical statistical difference was significant for all the factors affecting the drug entrapment efficiency of the formulated dipyridamole microballoons as the p-value was found to be<0.05.

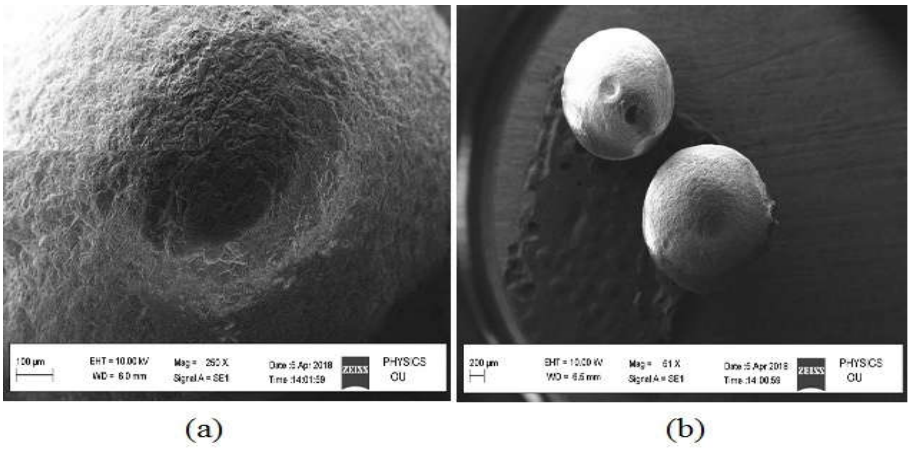

Fig. 3:SEM images of floating microspheres of formulation F34 indicating a) Surface morphology and b) Surface dents that indicate inside of the microspheres is hollow

Table 3: Anova for entrapment efficiency and Particle size of the dipyridamole microballoons

Response	Source	SS	Df	MSS	F–value	p–value	Inference
Entrapment	Model	1122.35	5	224.47	22.17	<0.0001	Significant
efficiency	A	313.29	1	313.29	30.95	<0.0001	Significant
	B	35.70	1	35.70	3.53	0.0688	Significant
	C	358.16	1	358.16	35.38	<0.0001	Significant
	D	91.20	1	91.20	9.01	0.0049	Significant
	E	324.00	1	324.00	32.00	<0.0001	Significant
	Residual	354.34	35	10.12			
Particle size	Model	3.290 x10^5	5	65800.52	29.43	<0.0001	Significant
	A	75680.01	1	75680.01	33.84	<0.0001	Significant
	B	8728.23	1	8728.23	3.90	0.0561	Significant
	C	72589.83	1	72589.83	32.46	<0.0001	Significant
	D	41575.21	1	41575.21	18.59	0.0001	Significant
	E	1.304Ex10^5	1	1.304Ex10^5	58.33	<0.0001	Significant
	Residual	78266.57	35	5.651x10^{-4}			

Floating characterization

Upon observing the buoyancy of all the formulated microballoons for a period of 24 h, the percent buoyancy of all the microballoons was found to be 85% and above as shown in table 2 indicating that the selected formulation and experimental conditions were suitable to develop floating microballoons. This was further evidenced by the results of SEM studies (fig. 3) that the microparticles had surface dents which indicated hollowness inside the particles.

Particle size and size distribution

Fig. 3 depicts the SEM analysis conducted for the formulation F34. SEM analysis pictures of fig. 3 indicate the presence of a smooth surface of the microballoons with the presence of surface dents inferring the presence of hollowness inside the microballoons.

It was inferred from fig. 4 that upon an increase in volume of internal phase, the particle size was found to be decreased which might be attributed to decrease in the viscosity of the internal phase at higher volume of solvent that might result in the fine globule formation in the emulsion, thus finally lead to the decrease in the size of the microspheres. With increase in polymer concentration, the particle size was found to be increased which might be due to the increased viscosity of the dispersion at high amount of polymer that might inversely affect the fine globule formation in the emulsion, hence lead to the increase in the size of the microspheres. This was evidenced by the results reported by Sharma N *et al.* [25].

It could be inferred from fig. 5 that upon increase in the concentration of surfactant, the particle size was found to be reduced, which may be attributed to the reduction of aggregation of globules in the emulsion. Upon increase in the speed of rotation, the particle size was found to

be reduced, which might be attributed to the more energy input into the emulsion at higher speed that must have lead to the formation of smaller globules in the emulsion, which finally might have lead to the formation of microspheres of smaller size upon evaporation of the solvent. The obtained results were correlated with the reports of Srikar G *et al.* [26]. From the results of ANOVA (shown in table 3), the effect of all the factors on particle size was found to be significant as the p-value is less than 0.05 for all the factors.

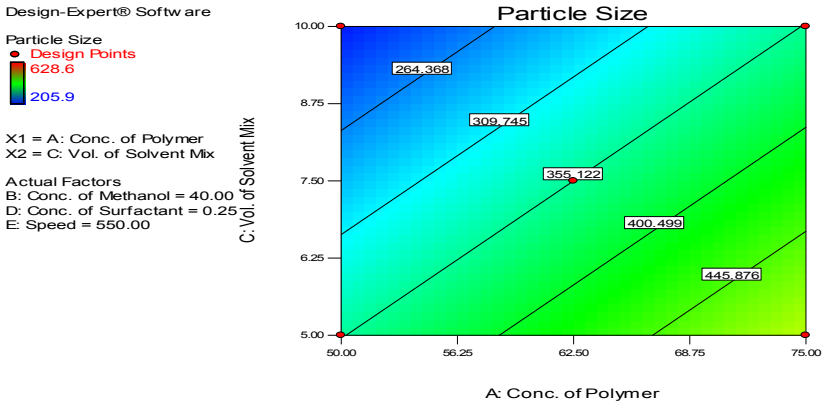

Fig. 4: Contour plot showing the effect of polymer concentration and volume of internal phase on particle size

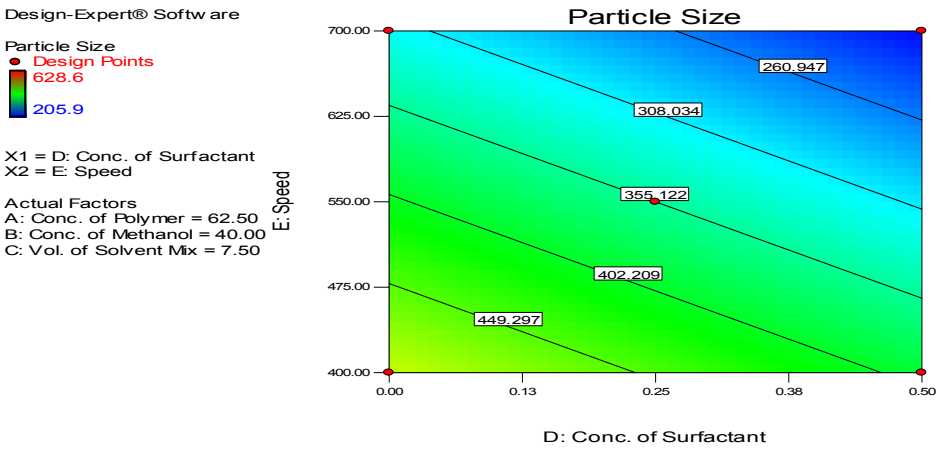

Fig. 5: Contour plot showing the effect of concentration of surfactant and speed on particle size

Drug release and release kinetic studies

The results of drug release studies and release kinetic studies were shown in table 4. Among all the formulations, F34 showed maximum control of drug release with a release rate constant of 0.096 hr^{-1} and F15 showed the least control with a release rate constant of 0.251 h. Drug release from all the formulations followed first-order kinetics and release mechanism was found to be non-fickian diffusion.

Table 4: Drug release kinetics of dipyridamole microballoons

S. No.	Formulation	Regression values			Peppas 'n' value	Drug release rate constant (k h)
		Zero-order	First-order	Higuchi		
1	F7	0.863	0.985	0.971	0.704	0.142
2	F21	0.904	0.992	0.941	0.81	0.145
3	F34	0.935	0.905	0.981	0.894	0.096

Experimental design validation and ANOVA

Box–Behnken design was used for the development of the dipyridamole microballoons as it is advantageous over the full factorial designs because in the full factorial design, the number of runs will increase when the number of factors and levels taken were increased where as in the box–Behnken design, the same conclusion of results can be obtained for a less number of trials. It can be inferred from table 3 that the model was found to be significant through statistical analysis by ANOVA as the p–value was found to be<0.05.

CONCLUSION

In the current work, we developed microballons with high entrapment efficiency and relatively small-sized particles. Influence of various formulation and process parameters on entrapment efficiency and particle size were studied. Entrapment efficiency is

one of the most important characteristics of particulate drug delivery systems and it decides the weight of the formulation to be taken in order to have the required dose. The experiment was designed according to Box–Behnken design under response surface methodology and performed. The obtained results suitably analyzed by ANOVA and found that all the selected factors were found to have a significant influence on entrapment efficiency and hence the major objective of the work was achieved.

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AUTHORS CONTRIBUTIONS

The research idea was set with guidance of Dr. A. Ramu, Prof. Dr. S. Vidyadhara. The research work was done by Seelam Ramya Krishna. The manuscript was prepared by Seelam Ramya Krishna and the critical revision of the manuscript was done by Dr. A. Ramu, Prof. Dr. S. Vidyadhara.

CONFLICT OF INTERESTS

Declare none

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