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Novel gastroretentive formulation of an Ayurvedic churna for peptic ulcers: Optimization and evaluation

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ABSTRACT: Avipattikar churna is well known Ayurvedic formulation in India for Amalpitta. Voluminous dose leading to poor patient compliance, less residence time in stomach and less stability are the major limitations of the Churna. Thus, the objective of research work was to develop a novel gastroretentive floating drug delivery system of Avipattikar churna. The churna was prepared and evaluated for phytochemical analysis. The main constituents, Jalap, and Clove, contained scopoletin and eugenol as active markers. A floating tablet of Avipattikar churna was optimized using a 3^2 factorial design, with HPMC K4M and HPMC K100M concentrations as independent factors and floating lag time (FLT) and % release of scopoletin and eugenol at 1 h, at 4 h and at 8h as dependent variables. The optimized formulations were evaluated by physical parameters. The optimized formulation was selected based on factorial design and numerical desirability Index values. *In-vitro* dissolution study was performed for optimized formulation and compared with marketed Avipattikar churna. Release mechanisms of markers were determined using various kinetic models and DD solver. The stability studies followed ICH guidelines. The preliminary trial batches were formulated by using direct compression method. 15% of the mixture of HPMC K100M and HPMC K4M was finalised based on the factorial design results and desirability index. Optimized formulation showed FLT of 88 ± 0.3 sec, with cumulative eugenol release at 1h (18.78%), 4h (60.23%), and 8h (95.36%). Scopoletin cumulative release was 21.43%, 68.51%, and 89.34% at 1h, 4h, and 8h, respectively. In a release kinetics, formulation showed diffusion mechanism followed by anomalous diffusion. The formulation was stable as revealed by 3 months accelerated stability studies as per ICH guidelines. From the experiments, 15% of HPMC K100M and HPMC K4M gave shorter floating lag time, good consistency and extended the duration of drug release over time frame of 8h. The formulation was found to be stable.

KEYWORDS: Gastroretentive floating tablet; Avipattikar churna (An Ayurvedic classical formulation); 3^2Factorial design; Drug release

1. INTRODUCTION

In Ayurveda, the treatment of Avipattikar Churna was found to be effective in treating peptic ulcers and GI-related problems like hyperacidity, piles, etc [1] (Ayurvedic pharmacopoeia of India 2007). The formulation was to have cytoprotective action, decreasing acid secretion and promoting mucus production and mucosal resistance. It was also shown aid in maintaining the basal blood flow to the gastrointestinal mucosa [2-6].
To overcome the limitations of Ayurvedic churna, Alternative dosage forms are essential that can be easily administered, provide patient compliance, and also provide gastroprotective action [7].
The oral route is recommended method of pharmaceutical administration because it offers low administration difficulty, the correct dose, a precise, flexible dosing schedule, self-medication, and desirable patient compliance [8, 9]. A better way to deal with these issues could be to produce gastro-retentive formulations to ensure patient compliance, ease of administration and reducing dose. A prolonged release of the drug is made possible by FDDS (floating drug delivery systems) having lower bulk density in comparison to gastric fluids and hence float in the stomach without slowing down the gastric emptying rate [10, 11]. More specifically, CO2 gas is produced by the effervescent varieties of floating drug delivery systems, which lower the density of the system and allow it to float in the stomach for a prolonged period of time while gradually releasing the drug at a sustained and constant rate [12, 13]. These medication delivery systems are designed to provide medication to the upper gastrointestinal tract over a sustained period of time [14, 15].

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So, the rationale of the experimental work was to design, develop, and evaluate the gastro-retentive floating tablets of the in-house Avipattikar churna by using different combinations of hydrophobic (glyceryl benehate), hydrophobic-hydrophilic (glyceryl benehate and HPMC K4M), and hydrophilic-hydrophilic (HPMC K4M and HPMC K100M) polymers. Optimisation of polymer combinations at different concentrations of the total polymer ratio was performed to increase the floating duration for a desirable time.

2. RESULTS AND DISCUSSION

2.1 Physicochemical evaluation of in-house Avipattikar churna

The churna was evaluated by physicochemical parameters. In physicochemical parameters LOD (4.4 %w/w), alcohol extractive value (23.8%w/w), aqueous extractive value (67.4% w/w), hydroalcoholic extractive value (59.8%w/w) and pH of aqueous suspension of churna (4.2) were noted and all were found within the limit specified by API [1]. UV spectroscopy results indicated that the presence eugenol and scopoletin was 0.12%w/w and 0.0389%w/w respectively in-house Avipattikar churna.

2.2 Evaluation of preliminary floating tablets

The preliminary trial batches (uncoated tablets of P1-P5) were evaluated for characterization and the outcome is represented in Table 1. The results clearly revealed that hydrophobic polymer (glyceryl behenate) alone or combination of hydrophobic and hydrophilic polymer (glyceryl behenate: HPMC K4M) failed to produce required in-vitro buoyancy and hence are not suitable candidates for final batch optimization. The preliminary batches (P6-P9) results represented in Table 1 justified the blending of hydrophilic polymers (HPMC K100 M: HPMC K4M). The results also revealed requirement of higher concentration of HPMC K100 M in comparison to HPMC K4M for good In vitro buoyancy and rapid floating.

Table 1. Results of preliminary trials of different batches by using different polymers

Sr. No.	**P1**	**P2**	**P3**	**P4**	**P5**	**P6 (30% w/w)**	**P7 (25%w/w)**	**P8 (20% w/w)**	**P9 (15%w/w)**
Type of matrix	**Hydrophobic matrix based Tablet**			**Hydrophobic - Hydrophillic matrix based Tablet**		**Hydrophillic matrix based tablets**			
Churna	800	800	800	800	800	800	800	800	800
Glyceryl benehate	120	240	350	150	300	-	-	-	-
HPMCK100M	-	-	-			250	195	193.6	139.2
HPMC K4 M	-	-	-	150	200	170	130	48.4	34.8
Sodium bicarbonate	140	200	100	150	100	100	100	100	100
MCC PH 101	70	100	70	80	50	60	60	48	66
Aerosil 200	10	10	10	10	10	10	10	10	10
Mg stearate	-	-	-	10	10	10	10	10	10
Total weight	1140	1350	1330	1350	1470	1400	1300	1210	1160
Floating lag time	No floating	No floating	No floating	No floating	No floating	21 Sec	53 Sec	30 sec	88 sec
Tablet Integrity	1.5 h	2.8- 2.9 h	4.6- 4.8 h	2-2.1 h	3.5-3.9 h	> 8 h	7 h 21 mins	> 10 h	> 8 h

2.3 Formulation of gastro retentive tablets using 3^2 full factorial design

The formulation optimization was done by using the concentrations of HPMC K100M (A) and HPMC K4M(B) as independent variables (with a concentration of 111.36 (-1), 139.2(0), 167.04(+1) and 27.84 (-1), 34.8(0), 41.76(+1) respectively) and 1 hr, 4hr, 8hr dissolution time-points (%drug release at Q1, Q4 and Q8) and Floating lag time (min) as dependent variables. During 3 months stability analysis at various conditions as per ICH guidelines, all 9 batches were found compliant.

Comparative *In vitro* buoyancy results of factorial batches F1-F9 shown in Fig 1. Reaction between gas forming agent and dissolution media leads to evolution and entrapment of CO2 inside the hydrophilic polymer matrixes results into decrease in matrix density and finally floating of the tablet. An *In-vitro* buoyancy study revealed that all batches from F1 to F9 have floating lag time less than 129 seconds (Table 2). On the other hand, swelling of HPMC K4M and HPMC K100M produced by an increase in tablet volume due to the solvent penetrating polymer layer led to a net drop in tablet density, extending the floating duration to more than 8 hours. In all the batches, tablets were found swollen and tablet integrity was intact.

Table 2. Results of Post compression parameters

Formula #	Thickness (mm) n=6	Hardness (kg/cm2) n=6	Friability (%) n=10	Average weight variation n=20	Floating lag time (Sec) (±SD, n=3)	Floating duration (hrs)	Tablet shape
F1	7.33 ± 0.10	12.2 ± 1.86	0.34 ± 0.08	1160.5 ± 9.19	128 ±0.2	> 8 hr	Swollen and Retained integrity
F2	7.32 ± 0.18	11.6 ± 2.67	0.35 ± 0.06	1160.4 ± 11.69	122 ±0.5	> 8 hr	Swollen and Retained integrity
F3	7.35 ± 0.12	11.2 ± 1.08	0.38 ± 0.02	1160.3 ± 8.52	108 ±0.6	>8 hr	Swollen and Retained integrity
F4	7.37 ± 0.13	10.2 ± 1.77	0.33 ± 0.07	1160.9 ± 10.61	96±0.6	> 8 hr	Swollen and Retained integrity
F5	7.31 ± 0.08	12.5 ± 1.34	0.33 ± 0.02	1160.0 ± 8.25	88 ±0.3	> 8 hr	Swollen and Retained integrity
F6	7.30 ± 0.13	10.4 ± 2.57	0.36 ± 0.04	1160.9 ± 9.29	78 ±0.5	> 8 hr	Swollen and Retained integrity
F7	7.29 ± 0.14	11.4 ± 1.36	0.32 ± 0.08	1160.5 ± 10.44	55 ±0.9	> 8 hr	Swollen and Retained integrity
F8	7.38 ± 0.09	12.3 ± 1.92	0.20 ± 0.03	1160.7± 9.64	45 ±0.8	> 8 hr	Swollen and Retained integrity
F9	7.39 ± 0.16	10.4 ± 2.01	0.32 ± 0.06	1160.8 ± 12.54	32 ±0.4	> 8 hr	Swollen and Retained integrity

2.3.1 In vitro dissolution studies

The *In vitro* drug release profile of F1-F9 represented in Figure 1. The statistical data (ANNOVA) of key chemical tests are tabulated in Table 3. The p value < 0.05 were considered significant and included in the model. 3D surface responses of dependent variables were portrayed in Figure 2 along with overlay contour plots in Fig 3. The results of release profiles revealed that the polymer concentration, negatively affects release of phytoconstituents at 1 h (Q1), 4 h (Q4) and 8 h (Q8) and positively affect FLT. The Q4 results showed wide variation ranging from 38.28 %-83.67% for, Eugenol and from 42.32%-82.21% for scopoletin. Higher the polymer concentration, higher was the viscosity of the matrix's gel layer in tablet leading to prolonged diffusion path. The related results were stated by Hiremath et al (2008) [16] for Isoniazid tablet. It is also clear from the results of Figure 1, contour plots (Figure 2) that concentration of HPMC K100 M was the most influencing factor for Q1, Q4, Q8 and FLT in comparison to concentration of HPMC K4 M. The plausible explanation has been the polymer viscosity of the matrix, as the concentration of HPMC K100 M increases, viscosity of matrix increases and induces higher chain entanglement and reduces the release of phytoconstituents. The results also indicated initial burst release followed by sustained release. This action is thought to be caused by the rapid surface drug dissolution off the matrix surface followed swelling and construction of protective gel layer. Similar results were obtained by Ram HN et al (2010) [17] for Liquorice floating tablet.

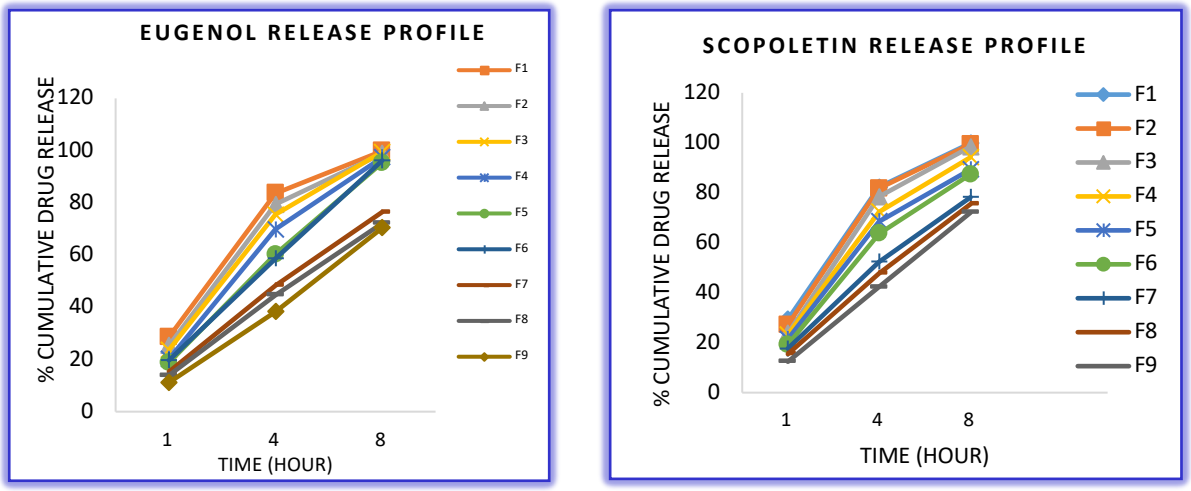

Figure 1. % Cumulative drug release profile of eugenol and scopoletin

It was also observed in the results that at the lower level of HPMC K100 M (-1) more than 75% release of scopoletin and eugenol was observed suggesting failure to achieve sustained release up to 8 hr. This might be due to formation of weak matrix and higher absorption of water subsequently diminishing matrix strength and ultimately releasing higher amount of scopoletin and eugenol. On the contrary the higher level of HPMC K100 M (+1) produces strong matrix but could not release more than 85% of scopoletin and eugenol at 8 hrs suggesting insufficient release at 8 hrs. It was cleared from results that both the polymers had negative effect on floating lag time and as polymer concentration increases FLT decreases. Out of the two polymers, HPMC K 100 M had the highest effect on the reduction of floating lag time (Table 3). Sodium bicarbonate releases carbon dioxide after reacting with gastric fluid. The evolve gas entrapped into swollen matrix and provide buoyancy to the matrix tablet. HPMC K100M having high viscosity (100000 cps) in comparison to HPMC K4 M (4000 cps) and showed higher swell ability and slower FLT. The results are in accordance with the results obtained by Djebbar et al (2020)[18].

Table 3. ANNOVA table of response

Equation	Q1	Q4	Q8
Eugenol	Q1= +19.61 – 6.21* A – 1.59 * B	Q4= = +62.04 – 17.87*A – 4.91*B	Q8= +95.52 – 13.18*A – 1.26*B – 1.44*AB -10.12*A^2 + 1.17*B^2
Scopoletin	Q1= +21.06 – 5.78*A – 2.49*B	Q4= +68.66 – 16.64 * A – 3.77* B -1.58*AB- 4.02*A^2 - 0.76* B^2	Q8= +88.27 – 11.99*A –2.40*B
FLT	Floating lag time = +88.77 – 37.67 * A – 10.17* B - 0.75 * AB - 2.17 * A^2 - 5.67 * B^2		

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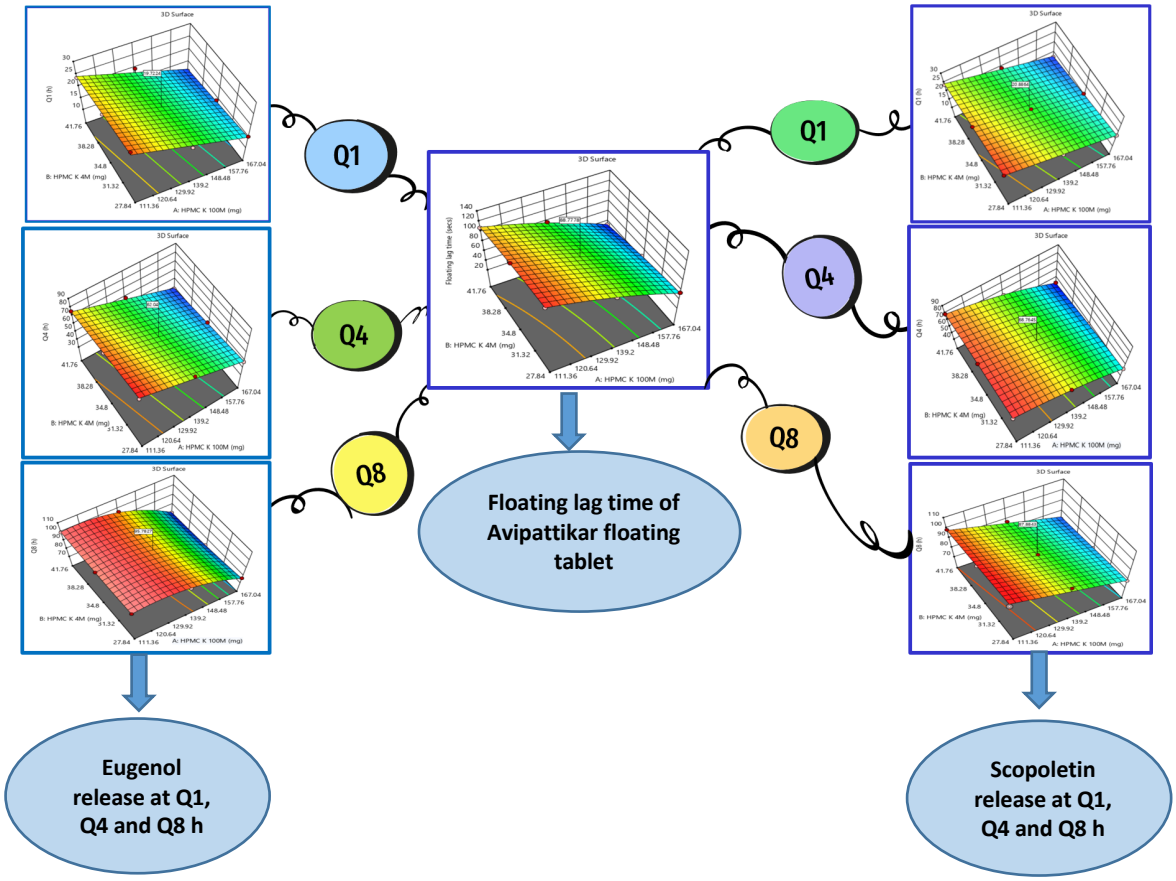
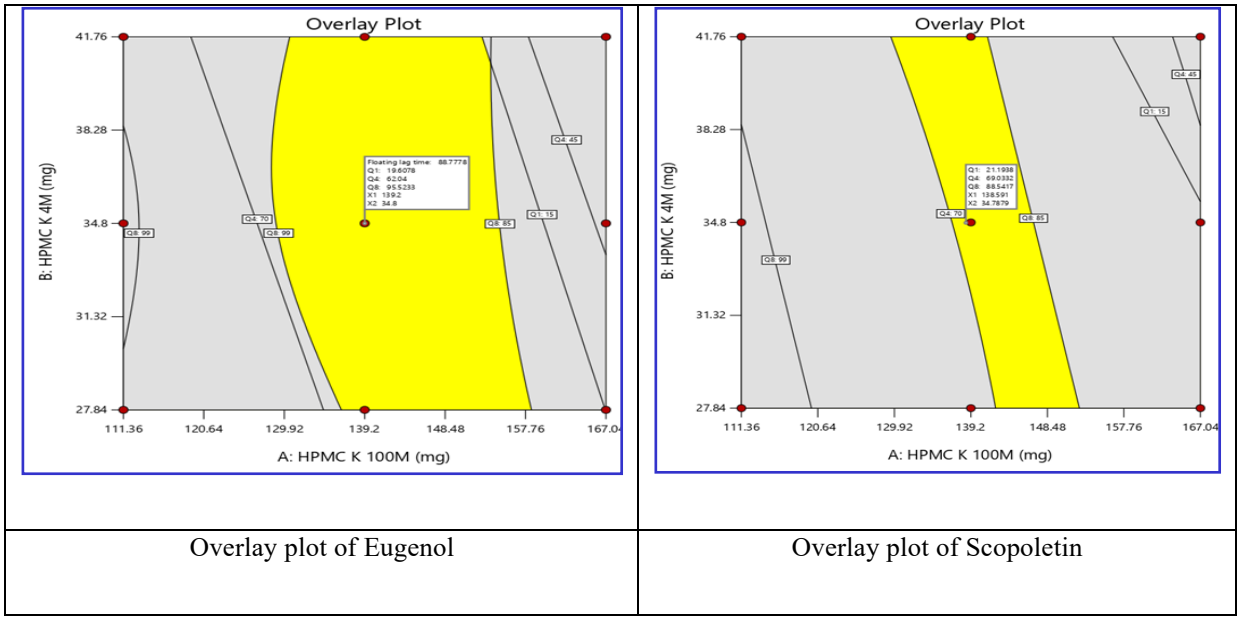


Figure 2. 3D surface responses of dependent variables FLT, Q1, Q4 and Q8 for Eeugenol and scopoletin



Overlay plot of Eugenol	Overlay plot of Scopoletin

Figure 3. Overlay plot for Eugenol and Scopoletin Release of optimized batch

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2.3.2 Checkpoint analysis

For confirming trustworthiness of model, the key chemical parameters were varied beyond the model prediction in two trials. The forecasted and actual results of these trials for the key chemical parameters are summarized in Table 4. Equation 1 was used to calculate bias or percent relative error between forecasted and actual response of each parameter. Reasonable agreement among the experimental and forecasted results confirmed the developed model validation.

Table 4. Comparison of responses between predicted and experimental values for the cross validation set.

Responses	Drug	Test	Factors/ levels (coded values)		Experimental values	Predicted values	Bias(%)
Floating lag time	-	1	0.8	(-0.7)	65.18	62.47	-4.33808
		2	(-0.7)	0.8	105.45	107.07	1.513029
Q1	Eugenol	1	0.8	(-0.7)	15.15	15.75	3.809524
		2	(-0.7)	0.8	23.02	22.68	-1.49912
Q4		1	0.8	(-0.7)	52.91	51.23	-3.27933
		2	(-0.7)	0.8	67.89	70.61	3.852146
Q8		1	0.8	(-0.7)	89.01	85.86	-3.66876
		2	(-0.7)	0.8	99.95	103.73	3.644076
Q1	Scopoletin	1	0.8	(-0.7)	18.75	18.17	-3.19207
		2	(-0.7)	0.8	22.34	23.1	3.290043
Q4		1	0.8	(-0.7)	55.45	57.98	4.363574
		2	(-0.7)	0.8	75.23	77.28	2.652692
Q8		1	0.8	(-0.7)	82.04	80.35	-2.1033
		2	(-0.7)	0.8	98.01	94.74	-3.45155

2.3.3 Desirability index (DI)

Floating lag time, % drug release (eugenol and scopoletin) at 1hr, 4hr and 8hr were collated to determine desirability function. Each variable value was assigned weightage and significance 1 respectively. From the results of batch 5 and 6, were shown nearer results to 1. However, total polymer concentration in batch F5 is less in comparision to batch F6 and hence, batch F5 (15% total polymer concentration) was selected as optimum batch. Composite desirability value and over lay contour plots identifies batch F5 as the best suited batch having DI of 0.70 (Table 5).

2.3.4 Curve fitting and release mechanism

Table 6 summarizes the results of adjusted R^2, AIC and MSC for various release kinetics models of optimized batch F5 after applying DD Solver. The dissolution profile of the optimized batch F5 was perfectly fitted to the Korsmeyer–Peppas' power law release kinetics in comparison to other release models, upon co-relating the values of adjusted r^2 for eugenol and scopoletin with that of the other models (Figure 4). Importantly, the adjusted r^2 value was used to assess goodness of fit instead of observed r^2 because observed r^2 always rises upon adding further variables, however r^2 adjusted is likely to fall once over fitting has taken place. To make the comparison more reliable and to nullify effect of other parameters, AIC was also recorded as a measure of fit for excellence for each release models. The results clearly indicated highest adjusted R^2 value, lowest AIC and highest MSC for peppas' release model. Hiremath et al (2008)[16] reported similar results for Isoniazid tablets. The results of Korsmeyer–Peppas release exponent (n) calculated for the optimized batch F5 are 0.773 and 0.675 indicates the likely release by anomalous transport. The n value in Korsmeyer–Peppas model for the optimized batch F5 was found to be 0.773 and 0.675 for eugenol and scopoletin indicating the likely release by anomalous transport (Table 6). The release mechanism of phytoconstiuents from hydrophilic tablet is complex mechanism combining both diffusion of phytoconstituents, chain relaxation and simultaneous erosion of matrix tablet, changing diffusion path length continuously. Similar release results were obtained by Hiremath and Saha 2008. Initial burst release of eugenol and scopoletin could be explained due to presence of surface drug on matrix tablet. Results obtained are in accordance with the results shown by Vora et al 2013 [19]. The dissolution results of optimized batch is compared with dissolution of churna. Sustained release of scopoletin and eugenol were observed in case of optimized batch in comparison to pure churna as depicted in Figure 4.

Table 5. Results of desirability index

	Eugenol			Scopoletin			FLT	
Formula	**DIQ1**	**DIQ4**	**DIQ8**	**DIQ1**	**DIQ4**	**DIQ8**	**DI**	**Total DI**
F1	1	0	1	1	0	1	0	0.6
F2	0.81	0	0.966	0.868	0	0.983	0.0625	0.5
F3	0.719	0	0.988	0.667	0	0.948	0.208	0.5
F4	0.52	1	0.916	0.638	0	0.797	0.33	0.6
F5	0.438	1	0.849	0.533	1	0.621	0.417	0.70
F6	0.485	1	0.877	0.403	1	0.551	0.521	0.70
F7	0.236	0	0.207	0.312	0	0.221	0.760	0.2
F8	0.157	0	0.0605	0.180	0	0.122	0.865	0.2
F9	0	0	0	0	0	0	1	0.1

Table 6. Comparative characteristics of different drug release kinetic models for optimized batch

Optimised batch	Zero order	First order	Higuchi	K-Peppas
		Eugenol		
Adjusted R^2	0.6965	0.9432	0.9523	0.9585
AIC	58.4548	44.5659	43.6455	43.3027
MSC	0.9422	2.6145	2.7934	2.8363
		Scopoletin		
Adjusted R^2	0.9360	0.9409	0.8937	0.9797
AIC	49.2052	48.5745	53.2710	40.8063
MSC	2.4993	2.5781	1.9911	3.5492

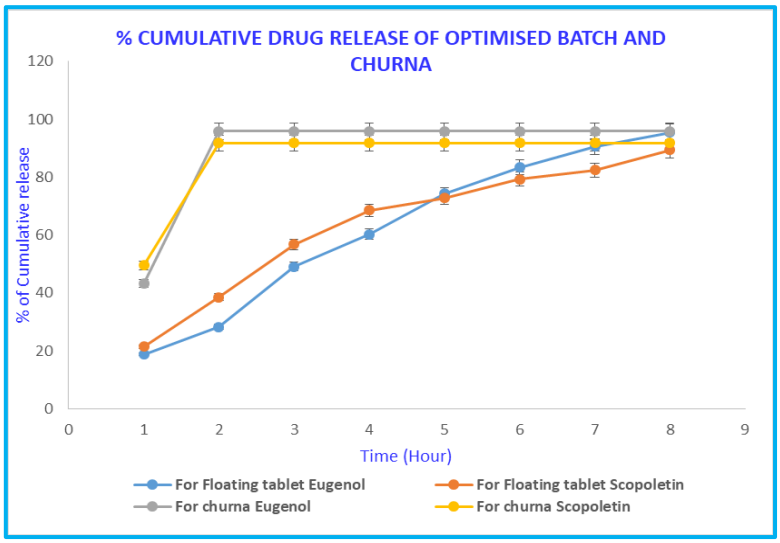

Figure 4. % Cumulative release of optimised batch

2.4 Stability study

The optimised formulations barely changed for factors including appearance, hardness, estimation of phytoconstituents, floating lag time, and dissolution under storage circumstances. The similarity factor (f2) was calculated for assessment of dissolution profiles on different time points (Q1, Q4 and Q8) using DD solver. f2 value for eugenol and scopoletin were found to be 80.021and 81.386 respectively suggesting that the stability of formulation.

3. CONCLUSION

The aim of the current study was to develop and assess gastroretentive tablets using different polymer and Avipattikar churna combination. From the findings of the preliminary results, hydrophilic polymers

were found to be more matrix-forming with churna than hydrophilic-hydrophobic polymers and alone hydrophobic polymers. Factorial batches were prepared by using different concentration of HPMC K4M and HPMC K100M while floating lag time, %dissolution at 1 h, 4h and 8h. All the batches passed the initial parameters, and the total floating time exceeded 8 hours. Based on the findings, it was determined that the diffusion mechanism followed by sustained drug release happened as a result of matrix formation. The maximum desirable values of FLT and %CDR at Q1, Q4 and Q8 h were obtained of batch F5. The mathematical model developeded by factorial design was also validated by preparing checkpoint batches. The regulated release of the several phytoconstituents in the formulation helped to overcome the churna's restriction. The result indicated that the dose reduction of churna might be possible after thorough clinical trials.

4. MATERIALS AND METHODS

4.1 Materials and Instruments

Shunthi, Pippali, Maricha, Vibhitaka, Haritaki, Amlaki, Musta, Salt, Ela, Vidanga, Patra, Lavanga, Jalap and sugar candy were procured from the local market, Ahmedabad, India. Glyceryl behenate (Gattefosse, Mumbai), HPMC K4M, HPMC K100M (Merck, Mumbai, India) were procured. Microcrystalline cellulose (Avicel pH 102), magnesium stearate, sodium bicarbonate, aerosil and hydrochloric acid were obtained from SD Fine Chemicals, Mumbai, India. Other all reagents were used of analytical grade.

Instruments: FTIR spectrophotometer (Shimadzu Corporation Kyoto, Japan), electronic balance (Shimadzu AX 120, Japan), sieve 60# (Jayant Scientific Industries, Mumbai, India), electronic parity (Shimadzu AX 120, Japan), Roche friability apparatus (Scientific Engineering Corporation, Delhi, India), UV spectrophotometer (Shimadzu, Kyoto, Japan), monsanto tablet hardness tester, USP 34 type II dissolution apparatus (VDA 6-DR, Veego Instruments Corp., Mumbai, India), Tablet compression machine (8 station rotary compression machine, model engineering works, New Delhi).

4.2 Preparation and physicochemical evaluation of in-house Avipattikar churna

Avipattikar churna was manufactured in house as per the method described by the Ayurvedic Pharmacopoeia of India (API) (2007). It contains Pippali (*Piper longum*) Shunthi (*Zingiber officinale*), Maricha (*Piper nigrum*), Vibhitaka (*Terminalia bellerica*), Haritaki (*Terminalia chebula*), Amlaki (*Emblica officinalis*), Musta (*Cyperus rotundus*), Vida Lavana salt, Ela (*Amomum subulatum*), Patra (*Cinnamomum tamala*), Vidanga (*Embelia ribes*), Lavanga (*Syzgium aromaticum*), Jalap (*Operculina turpethum*), and Sharkara (Sugar candy). They were weighed separately, powdered, and mixed in 1 part with the exception of lavanga, jalap, and sugar, which are mixed in 11, 44, and 66 parts, respectively. 10g of churna with water, either before or after meals, is the suggested regimen for treating G.I related problems. The in house churna was evaluated for phytochemical analysis including LOD, alcoholic, water and hydroalcoholic extractive values as per mentioned in API (2007). In composition Jalap and clove are found as a major ingredients and they contain scopoletin and eugenol as an active ingredients respectively. So these active ingredients were quantified by UV spectroscopy method developed by Shah et al. The quantification of eugenol and scopoletin was done by a developed analytical method at λmax 296 and 278.5nm, respectively [20].

4.3 Preparation of Floating Tablets by Direct compression method

4.3.1 Preparation of preliminary floating Tablets by using different polymers

Nine preliminary trial batches were prepared by using hydrophobic polymer (glyceryl behenate), hydrophobic hydrophilic polymer (glyceryl behenate: HPMC K4M) and hydrophilic polymer (HPMC K100M and HPMC K4M) as per the composition shown in table 1 for the selection of polymer. The floating tablets were prepared by direct compression where sodium bicarbonate was used as gas forming agent. Accurately weighed ingredients were shifted from screen 60# of ASTM grade and thoroughly mixed for around 12 minutes. Finally, magnesium stearate and aerosil were sifted from screen 60# of ASTM grade and used as glidant and lubricant while blending for 3 minutes. The homogenous mixture was compressed on tablet compression machine using a 20.3 x 10.5 mm punch to produce tablets containing 800 mg of Avipattikar churna per tablet. The tablets' floating lag time and total floating time were evaluated.

4.3.2 *In vitro* buoyancy

Total floating time (TFT) and floating lag time (FLT) were taken into consideration as in vitro buoyancy. The randomly taken tablets were kept in dissolution apparatus (USP 34 type II) with 900 mL of

0.1 N hydrochloric acid (HCl) at 37◦C ± 0.5◦C and 50 rpm. The FLT, was calculated as the amount of time needed for the formulation to rise on the surface of the dissolution media. The experiments were performed in triplicates.

4.4 Formulation of gastroretentive tablets using 3^2 factorial design

Using a 3^2 (two-factor; three-level) experimental design, the concentrations of HPMC K100M (A) and HPMC K4M(B) (with a concentration of 111.36(-1), 139.2(0), 167.04(+1) and 27.84(-1), 34.8(0), 41.76(+1) respectively) were chosen as independent variables, and Q1(% drug released in 1 hr), Q4 (% drug released in 4 hr), Q8 (% drug released in 8 hr), and Floating lag time (min) were chosen as dependent variables. Preliminary batches results were considered as base for finalizing the level of independent factors to the application of factorial design. The composition of all batches is depicted in Table 7. The tablets were formulated as per described in section 4.3.1.

Table 7. Matrix of the factorial design experiments

Sr. No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	**Churna**	800	800	800	800	800	800	800	800	800
2	**HPMC K100M**	111.36	111.36	111.36	139.2	139.2	139.2	167.04	167.04	167.04
4	**HPMC K4M**	27.84	34.8	41.76	27.84	34.8	41.76	27.84	34.8	41.76
5	**Sodium Bicarbonate**	100	100	100	100	100	100	100	100	100
6	**MCC PH 101**	100.8	93.84	86.88	72.96	66	59.04	45.12	38.16	31.2
7	**Aerosil 200**	10	10	10	10	10	10	10	10	10
8	**Mg stearate**	10	10	10	10	10	10	10	10	10
	Total	1160	1160	1160	1160	1160	1160	1160	1160	1160

The Design expert 13.0.1 Stat-Ease Inc., USA software used for optimization. The outcomes of independent parameters on measured responses and their interactions were described using the subsequent equation for mathematical model:

$Y = b_0 + b_1A + b_2B + b_{12}AB + b_{11}A_{12} + b_{22}B_{22}$

Where

Y= dependent variable

B_0= arithmetic mean response of the nine runs

b_1 and b_2= estimated coefficient for the factor A and B respectively

The major effects are the overall result of one factor going from low to high number at a time. Interaction terms b_{12} and b_{21} are interaction terms represent the change in response to simultaneous factor changes. All response parameters were statified by ANOVA analysis and if the P value were found < 0.05 indicated model is significant [21, 22].

Design Expert software was utilised for all statistical analyses of Design of experiments DOE. Main interaction plots, effect plots, residual plots, and contour plots were created with overlays. All experimental trials were randomised to eliminate any possibility of bias. The terms A_{12} and B_{12} were also included to check non linearity [23, 24].

4.4.1 Physical Characterization of prepared tablets

The compressed tablets were evaluated for appearance, weight variation, hardness and drug content. Tablets were selected at random from each batch and evaluated separately using an electronic parity. 20 tablets average weight and weight variation were calculated and checked with IP limit. Tablet hardness was determined by using minimum 6 tablets for each batch with Monsanto. Ten tablets were randomly selected from each group for the Friability test and were turned at 25 rpm for 4 minutes and reweighed post cleaning.

4.4.2 In vitro dissolution studies

Each batch dissolution was performed in 0.1 N hydrochloric acid (HCl) using a USP Type II Apparatus at controlled condition of 37 ± 0.5 °C and 50 rpm. The selected testing time for dissolution study were 1 h, 4 h, and 8 h. The withdrawn samples were clarified through Whatmann filter paper and then analysed for drug release by a validated first derivative UV spectrophotometric method. The content of eugenol and scopoletin were determined as per method described in section 4.2. To validate the experimental design and polynomial equations, an exhaustive search across the whole experimental domain

was done. The experimental results obtained were then quantitatively compared to the projected values. The formulations with the highest desirability values for selected response were located in the experimental region of the overlay plot and chosen as the optimised formulation.

4.4.3 Checkpoint analysis

Checkpoint batches were prepared by taking coded value of 0.8 and -0.7 HPMC K100M and HPMC K4M respectively and responses were measured. %bias was calculated by using following equation 1.

% Bias= [(Predicted value-Experimental value)/(Predicted Value)]----------equation 1

4.4.4 Desirability Index

The desirability index (DI) was put into application to combine results of various criteria in sole numerical criteria response and to forecast optimum level of independent factors. When a response's value was on target or at its best, its desirability was given a value of 1, and when it was completely unsatisfactory, it received a value of 0. Anticipated highest Q1 to attain rapid acid neutralization and desirability for Q1 can be calculated by using following equation 2.

DI,Q1=(Yi-Ymin)/(Ymax-Ymin) ----------equation 2

Yi is the experimental value, and Ymax and Ymin are the maximum and minimum obtained values respectively. Ymin and Ymax for Q1, eugenol responses were 11.16 and 28.57 percent Eugenol release respectively as per the release study data (Figure 1).

No formal procedures are there for obtaining highest or lowest extreme value for Q4. Q4 results support the churna's sustained release from the dosing form. Formulations with percentage releases between 55% and 70% were deemed optimal and had an attractiveness score of 1, while formulas with values outside of this range had a score of 0. DI for Q8 was again calculated by using equation 2 where 70.38 and 99.82 percent Eugenol release were considered as minimum and maximum value (Figure 1).

Minimum Floating lag time was required for optimized product. The DI for FLT was calculated using following equation (3) considering 32 sec and 128 sec as minimum and maximum values respectively (Figure 1).

DI,FLT=(Ymax-Yi)/(Ymax-Ymin) ---------- equation 3

The overall DI for Eugenol was calculated by taking arithmetic mean of DI (Q1), DI (Q4), DI(Q8) and DI (FLT). Similar calculation was done for Scopoletin. The formulation exhibiting highest DI for all selected responses were considered as optimized batch [19].

4.4.5 Curve fitting and release mechanism

To explain the drug release kinetic profile, the % cumulative in vitro drug release were exposed to various kinetic models like zero-order, first-order, Higuchi, and Korsemeyer-Peppas [25-28]. The adjusted correlation coefficients (r^2), Akaike information criterion (AIC) and Model selection criteria (MSC) were used to determine the best model suit and calculation was done by using DD solver [29].

4.5 Stability studies

The stability studies of optimized batch were performed as per ICH guidelines (ICH Q1A(R2), 2003). The floating tablets of optimized batch were filled into the HDPE container along with silica bag as desiccant. The container was sealed and exposed to accelerated stability studies for 3 months at 40 ± 2 °C and 75 ± 5% RH (relative humidity)[30]. The withdrawn samples were evaluated for different physical and chemical parameters periodically. For comparative evaluation of in-vitro drug release profiles on each time point, the similarity factor (f2)[25] was applied.

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