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Development and Evaluation of Gastro Retentive Floating Tablets of Ayurvedic Vati Formulation

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***Abstract*—**Floating tablets of Marichyadi Vati were developed with an aim to prolong its gastric residence time and increase the bioavailability of drug. Rapid gastrointestinal transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of the administered dose. The tablets were prepared by wet granulation technique, using HPMC E50 LV act as Matrixing agent, Carbopol as floating enhancer, microcrystalline cellulose as binder, Sodium bi carbonate as effervescent agent with other excipients. The simplex lattice design was used for selection of variables for tablets formulation. Formulation was optimized on the basis of floating time and in vitro drug release. The results showed that the floating lag time for optimized formulation was found to be 61 second with about 97.32 % of total drug release within 3 hours. The vitro release profiles of drug from the formulation could be best expressed zero order with highest linearity $r^2 = 0.9943$. It was concluded that the gastroretentive drug delivery system can be developed for Marichyadi Vati containing Piperine to increase the residence time of the drug in the stomach and thereby increasing bioavailability.

***Keywords*—**Piperine, Marichyadi Vati, Gastroretentive drug delivery, Floating tablet.

I. Introduction

MARICHYADI Vati is one of the best classical formulations mentioned in Ayurvedic formulary of India and widely used in cough and asthma. The daily dose of formulation is 3 Gms as per Ayurvedic Formulary. The Vati contains piper nigrum and piper longum as main ingredients which contain Piperine as major Phyto-constituents. According to pharmacological studies it was reported that Piperine has toxicity in stomach. The principle of buoyant preparations offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. In this study floating drug delivery system (FDDS) is chosen as a method to obtain sufficient bioavailability and maintain therapeutic drug levels. As per the literature it is noted that no one has try to reduce the toxicity of Piperine and it is first attempt to develop NDDs of such Ayurvedic formulation. The aim of the present research study is to develop gastroretentive drug delivery system for Marichyadi Vati using simplex lattice design as an optimization technique [1].

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II. Materials and Methods

A. Materials

Marichyadi Vati was prepared in laboratory and its individual components were procured from, Ms. Sanjivani Ausadhalay, Bhavnagar. The Piperine was obtained from department of Pharmacognosy SKPCPER, Ganpat University, Mehsana, Gujarat, India.

B. Methods

1. Preparation of Stock Solution and Determination of Absorption Maxima of Piperine in 0.1N HCl

10mg of Piperine was dissolved in 1ml of methanol and then q.s. to 10ml with 0.1N HCl. 1ml of this solution was further diluted to 10ml in volumetric flask with 0.1N HCl. This was serving as a standard stock solution (100µg/ml). The spectrum of the Piperine was obtained by scanning this solution in the range of 200nm- 400nm against 0.1N HCl as blank to fix absorption maxima.

C. Calibration Curve

Calibration curve were established with eight dilutions of standard prepared from standard stock solution using further dilution, at concentration range from 2 to 16µg/ml. Each concentration was measured in triplicate. The corresponding absorbance was plotted against the concentration of the marker. The reference substance employed was Piperine. The graph so obtained was shown in Fig. 1.

D. Simplex Lattice Design [2], [3], [6]-[8]

Simplex lattice design was adopted to optimize the formulation variables. In this design, three factors were evaluated by changing their concentrations simultaneously and keeping their total concentration constant. The simplex lattice design for a 3-component system is represented by an equilateral triangle in 2-dimensional space. Seven batches (S1-S7) were prepared: one at each vertex (A, B, C), one at the halfway point between vertices (AB, BC, AC), and one at the center point (ABC). Each vertex represents a formulation containing the maximum amount of 1 component, with the other 2 components at a minimum level. The halfway point between the 2 vertices represents a formulation containing the average of the minimum and maximum amounts of the 2 ingredients represented by 2 vertices. The center point represents a formulation containing one third of each ingredient. The amounts of matrixing agent (HPMC E50 LV), gas-generating agent (Sodium bicarbonate, X2), and floating enhancer (Ethyl cellulose, X3) were selected as independent variables. The formula was mentioned in Table I.

E. Granules Formulation for Tablets

Granules were made with mortar and pestle and suitable sieve. The extract was dried, powdered and properly mixed with diluents in pestle. Then the mixture was moistened with a granulating agent (10% solution of PVP in alcohol) until a coherent but not too damp mass was produced. The coherent mass was passed through sieve number 22 & 44. The resulting granules were dried in oven at not more than 60^{o}C. The prepared granules were evaluated for physicochemical parameters. The result so obtained was shown in Table II.

F. Preparation and Evaluation of Trail Batch for Formulation Optimization [6]-[16]

The tablets were prepared by direct compression method using 12mm punch on 8 station rotary tablet compression machine. It is concluded that all 7 batches failed during the test of floating lag time in 0.1N HCl. Tablets of all batches get disintegrated with in 2 to 3 minutes and did not floats so it was decided to change the formula. The formula was mentioned in Table III.

The granules were prepared according to method mention previously and tablets were prepared by direct compression method using 12mm punch on 8 station rotary tablet compression machine. It is concluded that only batch f3 has passed during the test of floating time in 0.1N HCl (61 sec.). Tablets of all batches get disintegrated with in 2 to3 minutes and did not float, so it was decided to that batch F3 was selected as optimized formula for tablet formulation.

G. Evaluation of Tablets [5]

The granules were evaluated for bulk density, tapped density, carr's index, Hausner's ratio and angle of repose. The tablets were evaluated for hardness thickness, friability, weight variation test and in-vitro dissolution studies. The result so obtained was shown in Table IV.

H. In vitro Dissolution Study

In-vitro release profile of the floating tablets was evaluated using rotating basket dissolution apparatus. 900ml of 0.1N HCl, maintained at 37±0.5^{0}C were used as dissolution media respectively, and the basket was rotated at a constant speed of 50rpm. The tablet was placed in the baskets. Aliquots of samples were withdrawn at the interval of 15 minutes for 3 hrs. The samples withdrawn were filtered, diluted suitably and analyzed at 342nm spectrophotometrically for drug release. The drug concentration was then calculated using the standard calibration curve. The result so obtained was shown in Table V.

I. Model Dependent Parameters [4]

To study the release kinetics, the data obtained from *in vitro* drug release studies were plotted in various kinetic models.

J. Zero Order Model

As cumulative amount of drug released vs. time, describes concentration independent drug release rate from the formulation

$$C = kot$$

where ko is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. The graph so obtained was shown in Fig. 2 and the result so obtained was shown in Table VI.

K. First Order Model

As log cumulative percent drug remaining vs. time, describes concentration dependent drug release from the system.

$$LogC = LogC0 - kt/ 2.303$$

where C0 is the initial concentration of drug and k is the first order constant. The graph so obtained was shown in Fig. 3 and the result so obtained was shown in Table VI.

L. Peppas Model

A simple semi empirical model relating exponentially the drug release to the elapsed time (t)

$$Qt/Q\alpha = K_k t^n$$

K_k is a constant incorporating structural and geometric characteristic of the drug dosage form and in is the release exponent, indicative of the drug release mechanism. The graph so obtained was shown in Fig. 4 and the result so obtained was shown in Table VI.

M. Higuchi Model

As cumulative percentage of drug released vs. square root of time, described the release of drug based on Fickian diffusion as a square root of time dependent process from swellable insoluble matrix.

$$Q = kt1/2$$

where k is the constant reflecting the design variables of the system. The graph so obtained was shown in Fig. 5 and the result so obtained was shown in Table VI.

III. Results and Discussion

The major objective of the present study was to develop a gastroretentive drug delivery system for Marichyadi Vati using simplex lattice design as an optimization technique. In this study, tablets were prepared using HPMC E50 LV as matrixing agent, ethyl cellulose as floating enhancer, Sodium bicarbonate as effervescent agent and microcrystalline cellulose as excipients. Initially, seven trial batches (F1-F7) were prepared. It is concluded that all 7 batches failed during the test of floating lag time in 0.1N HCl. Tablets of all batches get disintegrated within 2 to 3 minutes and did not floats so it was decided to change the formula. The new variables were selected such as carbopol as floating enhancer and citric acid. The four trail batches (f1-f4) were prepared. It is concluded that only batch f3 has passed during the test of floating time in 0.1N HCl (61sec.). Tablets of all batches get disintegrated

with in 2 to 3 minutes and did not float, so it was decided to that batch f3 was selected as optimized formula for tablet formulation. The prepared tablets were evaluated for physicochemical parameters as hardness, thickness, friability, % weight variation and % drug content they all within the limit as per standard. In-vitro dissolution studies reveal that the % drug release at the end of 3 hrs was found to 97.32 % respectively. The in vitro release profiles of drug from the formulation could be best expressed Zero order as the plots (Fig. 2) showed highest linearity (r^2 = 0.9943) and it is concluded that formulation follows the Zero order kinetics of drug release which is best fitted for the pharmaceutical dosage form that do not disaggregate and release the drug slowly in order to achieve a prolonged pharmacological action.

IV. Conclusion

In this present work, attempt has made to prepare floating drug delivery with prolong gastric residence time. The release of Piperine from the formulation is proportional to the concentration of polymer. As the concentration of polymers increases, the drug release decreases. Results of the study based on in vitro performance clearly suggested that sustain release floating tablet can be prepared by incorporating sodium bicarbonate as effervescent agent with HPMC E50 LV polymer. Higher the concentration of bicarbonate faster is the drug release and shorter in the floating lag time and floating duration. On increasing the hardness of tablets resulted in significance increased in floating lag time.

TABLE I
Composition of Tablets According to Simplex Lattice Design

S. No	Batch No.	Dry Drug Extract (Mg)	Ethyl Cellulose (Mg)	HPMC E50 LV (Mg)	Sodium Bi Carbonate (Mg)	Microcrystalline Cellulose (Mg)	Lactose (Mg)
1.	**F1**	82	0	87.5	25	70	17.5
2.	**F2**	82	0	62.5	50	70	17.5
3.	**F3**	82	25	62.5	25	70	17.5
4.	**F4**	82	0	75	37.5	70	17.5
5.	**F5**	82	12.5	62.5	37.5	70	17.5
6.	**F6**	82	12.5	75	25	70	17.5
7.	**F7**	82	37.5	37.5	37.5	70	17.5

TABLE II
Evaluation Parameter for Granules

Bulk Density (G/Cc)	Tapped Density (G/Cc)	Carr's Index (%)	Hausner's Ratio	Angle Of Repose (Θ)
0.538	0.593	9.27	1.1	26.56

TABLE III
Optimization of Formulation According to New Variables

S. No	Batch No.	Dry Drug Extract (Mg)	HPMC E50 LV (Mg)	Carbopol (Mg)	Sodium Bi Carbonate (Mg)	Citric Acid	Microcrystalline Cellulose (Mg)
1.	**F1**	82	100	10	100	10	150
2.	**F2**	82	120	10	100	30	110
3.	**F3**	82	150	5	100	50	65
4.	**F4**	82	160	10	100	50	50

TABLE IV
Evaluation Parameter for Tablet

Hardness* (Kg/Cm^2)	Thickness* (Mm)	Friability* (%)	%Weight Variation*	% Drug Contents*
4.4	2.5	0.450	+3.8	97.49

TABLE V
IN VITRO DISSOLUTION STUDIES

Time (Min)	Absorbance	Conc. µg/Ml	Conc. µg/5ml	Conc. µg/900ml	Cumulative Drug Release (In Mg)	% Cumulative Drug Release
15	0.073	1.06	5.28	950	0.95	1.16
30	0.078	3.83	19.17	3450	3.46	4.21
45	0.085	7.72	38.61	6950	6.97	8.50
60	0.098	14.94	74.72	13450	13.49	16.45
75	0.11	21.61	108.06	19450	19.52	23.81
90	0.127	31.06	155.28	27950	28.06	34.22
105	0.135	35.50	177.50	31950	32.11	39.15
120	0.152	44.94	224.72	40450	40.63	49.55
135	0.168	53.83	269.17	48450	48.67	59.36
150	0.181	61.06	305.28	54950	55.22	67.34
165	0.198	70.50	352.50	63450	63.76	77.75
180	0.23	88.28	441.39	79450	79.80	97.32

TABLE VI
MODEL DEPENDENT PARAMETERS

Zero Order (R^2)	First Order (R^2)	Korsmeyer Peppas Model (R^2)	Higuchi's Model (R^2)
0.9943	0.9061	0.9671	0.9923

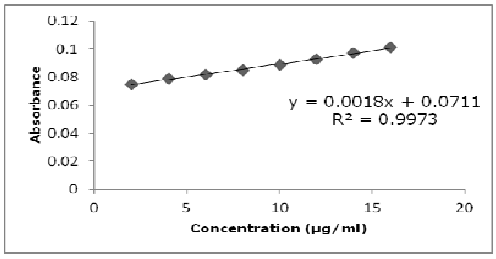

Fig. 1 Calibration curve of Standard Piperine in 0.1 N HCl at 342 nm

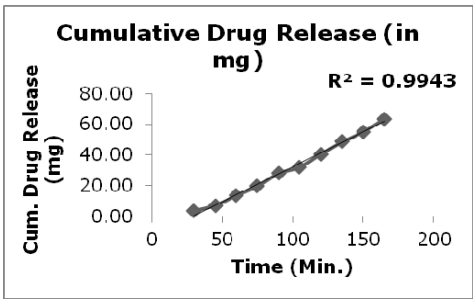

Fig. 2 Zero order model for drug release pattern

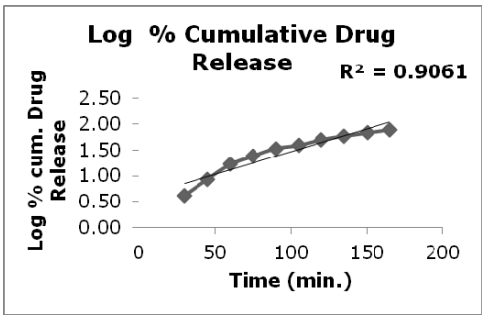

Fig. 3 First order model for drug release pattern

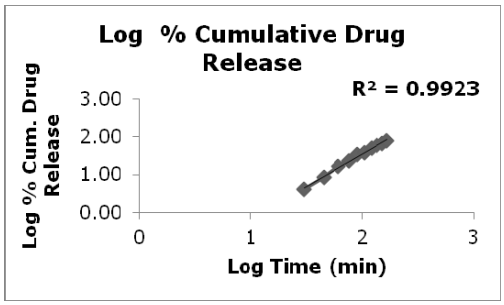

Fig. 4 Korsmeyer Peppas model for drug release pattern

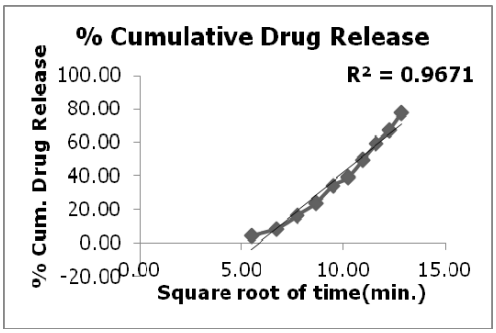

Fig. 5 Higuchi's model for drug release pattern

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