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Formulation, Development and Characterization of Sustained Release Formulation of Herbal Extracts

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Abstract

Aim: The aim of the present investigation is to design of sustained release dosage form of different extracts that will help in releasing only small quantities of drug over a prolonged period of time. **Material and Methods:** The different ingredients for formulations are given as in Table 1 below. The measured quantities of drug, HPMC, MCC and NaHCO3 were mixed thoroughly using a mortar and pistil. The granules were punched into tablets using direct compression technique. The blank formulation (or) placebo (HPMC+ MCC+NaHCO3) and polyherbal formulation were also tested using FTIR Spectrometer. The release rate kinetics of the formulations was analyzed and the data obtained were fitted into Zero order, First order, Higuchi model and Kozmeyer Peppas model. **Results:** The pre-formulation study results obtained on various parameters on granules were found satisfactory. The granules obtained for the batches (F1-F12) were satisfactory. No rat holing, capping or sticking was observed during the flow of granules from the hopper. The maximum weight variation of the tablets was±1.8%, which falls within the acceptable range of±5%, hence the tablets passed the weight variation test. Hardness for tablets of all batches was in the range of 4.92 to 5.35 kg/cm^2, which falls above the limit of not less than 3.0 kg/cm^2. The floating lag time ranged from 35 s to 50 s. From the Table 5, it was found that the formulation F11 has the minimum floating lag time of 35 s and maximum total floating time of 15 h with 100.12% drug content. **Conclusion:** The effect of ingredients in the polyherbal tablet was analyzed, where HPMC contributed as the floating matrix, MCC to increase the bulk density of the tablet and sodium bicarbonate to initiate the dissolution process.

Keywords: Buoyancy studies, Development and characterization, Formulation, Herbal extracts, Polyhedral tablet, Sustained release formulation

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Introduction

An ideal drug delivery system should aid in the optimization of drug therapy by delivering an appropriate amount to the intended site and at a desired rate. Hence, the DDS should deliver the drug at a rate dictated by the needs of the body over the period of treatment. An oral drug delivery system providing a uniform drug delivery can only partly satisfy therapeutic and biopharmaceutical needs, as it doesn't take in to account the site specific absorption rates within the gastrointestinal tract (GIT).[1] Therefore there is a need of developing drug delivery system that release the drug at the right time, at the specific site and with the desired rate.[2]

The main destination of any drug delivery system is to furnish a contributing to quantity of a drug to a suitable region in the body and that the required drug concentration can be attained promptly and then being maintained.[3] The drug delivery system should distribute a drug at a rate dictated by the require of the body for particular length of time. Sustained release tablets and capsules are mostly taken only once or twice daily, compared with immediate release tablet form that may have to take 3 or 4 times a day to attain the same required drug to produce the effect. Typically, the sustained release dosage form to furnish at once release the active component that give the what we are desired for cure of disease, followed by remaining quantity of drug should be release and maintained the therapeutic effect over a predetermined length time or prolonged period.[4]

The aim of the present investigation is to design of sustained release dosage form of different extracts that will help in releasing only small quantities of drug over a prolonged period of time.[5]

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Material and Methods

Sustained Release Formulation

For the preparation of sustained release formulation, we have selected floating drug delivery system. It is a type of sustained drug delivery system.

Preparation of Polyhedral Tablet

The different ingredients for formulations are given as in Table 1 below. The measured quantities of drug, HPMC, MCC and NaHCO3 were mixed thoroughly using a mortar and pistil. In order to obtain the granules, the mixture was passed through the 20 mm sieves. The granules were dried in a hot air oven and at last talc and magnesium stearate were added to the blend. The formulation of selected dosage form was given in Table 1.[6]

The granules were punched into tablets using direct compression technique. The blank formulation (or) placebo (HPMC+ MCC+NaHCO3) and polyherbal formulation were also tested using FTIR Spectrometer.

The standard parameters that have to be evaluated for prepared tablets were namely weight variation, hardness, friability, disintegration time and stability. In weight variation study, a random sample of twenty tablets was selected and the average weight was calculated.[7] Then this weight was compared with individual tablets weight. The hardness was measured using Pfizer hardness, where the tablets were placed in contact between the plungers and the force of the fracture was recorded. The friability was determined using Roche friabilator at a constant rpm. Six tablets from each formulation were tested.[8]

Evaluation Methods for Polyherbal Floating Tablets

In vitro buoyancy studies

The Polyherbal tablet was placed in a 100 ml beaker containing 0.1 N HCl. The time taken for the tablet to rise and float on the surface as floating lag time. The experiments were conducted in triplicate. Polyherbal effervescence tablet generates CO_2 gas thereby reducing the density and hence it remains buoyant for a prolonged time period releasing the drug slowly at the desired rate.[9]

In vitro dissolution studies

The release rate of polyherbal floating tablets was determined. The dissolution test was performed using United States Pharmacopeia (USP) type II paddle apparatus with an agitation speed of 50 rpm in 0.1 N HCL maintained at 37±0.5 °C. At appropriate time intervals, the samples were withdrawn and assayed spectrophotometrically using Elico double beam UV-visible spectrophotometer at λmax after filtration through Whatman filter paper and with suitable dilutions. The methodology for in vitro dissolution was kept the same for all the batches prepared. The experiment was done in triplicates.[10]

Rate kinetic studies

The release rate kinetics of the formulations was analyzed and the data obtained were fitted into Zero order, First order, Higuchi model and Kozmeyer Peppas model using equations in Table 2.[11]

Results And Discussion

It was found that the ethanol produces the maximum yield of 6.5% and 12.3% for all extracts.

Preformulation Studies

The pre-formulation study results obtained on various parameters on granules were found satisfactory. The granules obtained for the batches (F1-F12) were satisfactory. No rat holing, capping or sticking was observed during the flow of granules from the hopper.

The compressibility index and Hausner's ratio values obtained for granules of all the batches and were found to be in the range of 14.36-17.96 and 1.167–1.219 (<1.25) respectively as shown in Table 3. The prepared tablets were greenish brown coloured with a smooth surface having acceptable elegance.

Post Compressional Parameters

The maximum weight variation of the tablets was±1.8%, which falls within the acceptable range of±5%, hence the tablets passed the weight variation test. Hardness for tablets of all batches was in the range of 4.92 to 5.35 kg/cm^2, which falls above the limit of not less than 3.0 kg/cm^2. Friability value for tablets of none of the batch was more than 0.37%. The thickness of the tablets of all the batches was found in the range of 4.77-4.82 mm indicating fairly acceptable tablets as shown in Table 4.[12]

In Vitro Buoyancy Studies

The time taken for the tablets to rise to the surface and float is the floating lag time. The gas generated is trapped and protected within the gel, formed by hydration of the polymer, thus decreasing the density of the tablet. As the density of the tablet falls, the tablet became buoyant. The floating lag time ranged from 35 s to 50 s. From the Table 5, it was found that the formulation F11 has the minimum floating lag time of 35 s and maximum total floating time of 15 h with 100.12% drug content.[13]

Thus it was taken as the optimum formulation. Hence stability studies were carried out on F11 and there was a marginal increase of moisture content and hardness, while no change in the friability was found, showing that these changes were within the specified limits. The effect of ingredients in the polyherbal tablet was analyzed,

Table 1: Formulation of polyherbal effervescence floating tablet

Ingredients (mg)	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*	*F10*	*F11*	*F12*
Drug	250	250	250	250	250	250	250	250	250	250	250	250
HPMC K4M	---	---	120	120	---	---	140	140	---	---	160	160
HPMC K15M	120	120	---	---	140	140	---	---	160	160	---	---
MCC	165	130	165	130	145	110	145	110	125	90	125	90
NaHCO3	125	160	125	160	125	160	125	160	125	160	125	160
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5

*HPMC-Hydroxy propyl methyl cellulose, MCC-Micro crystalline cellulose

Table 2: Mathematical Models for drug dissolution

Model	*Mathematical equation*	*Release mechanism*
Zero Order First Order Higuchi Model	C=C0-K0t	Diffusion Mechanism
Kozmeyer Peppas Model	log C=log C0–K1. t/2.303	Fick's first law, diffusion mechanism
	Q0/Qt=KH. t1/2	Diffusion medium based mechanism in Fick's first law
	Ct/C=KK. tn	Semi-empirical model, diffusion based

Table 3: Evaluation parameter of powder blend

Code	*Angle of repose degree °*	*LBD gm/cm2*	*TBD gm/cm2*	*Compressibility index %*	*Hausner's ratio*	*Flow character*
F1	34.7	0.485	0.575	15.65	1.185	Good
F2	35.1	0.484	0.585	17.26	1.208	Fair
F3	35.6	0.478	0.582	17.87	1.217	Fair
F4	35.6	0.488	0.592	17.57	1.213	Fair
F5	35.1	0.495	0.578	14.36	1.167	Good
F6	34.2	0.487	0.572	14.86	1.174	Good
F7	34.6	0.492	0.581	15.31	1.181	Good
F8	35.5	0.485	0.579	16.23	1.194	Fair
F9	35.3	0.491	0.575	14.61	1.171	Good
F10	34.3	0.475	0.579	17.96	1.219	Fair
F11	35.1	0.494	0.583	15.26	1.180	Good
F12	35.5	0.490	0.581	15.66	1.186	Good

(Number of experiments n=3, mean), LBD-Loose Bulk Density, TBD-Tapped Bulk Density

Table 4: Evaluation parameter of tablet

Formulation Code	*Thickness (mm)*	*Hardness (kg/cm2)*	*Friability (%)*	*Average weight variation*	*Drug content (%)*
F1	4.65±0.096	5.10±0.191	0.36±0.010	500.1±1.304	100.02±0.334
F2	4.68±0.090	5.01±0.254	0.34±0.013	500.7±1.795	100.12±0.319
F3	4.72±0.128	4.92±0.157	0.37±0.017	499.0±1.633	100.00±0.191
F4	4.69±0.130	5.27±0.275	0.33±0.027	499.7±1.247	100.07±0.304
F5	4.78±0.111	5.18±0.219	0.37±0.016	500.3±1.699	100.03±0.320
F6	4.73±0.118	5.35±0.096	0.35±0.019	500.6±1.367	100.18±0.121
F7	4.65±0.108	5.33±0.197	0.33±0.019	500.1±0.837	100.10±0.129
F8	4.73±0.099	5.25±0.171	0.36±0.021	500.3±0.804	100.18±0.381
F9	4.70±0.071	5.05±0.096	0.35±0.023	500.9±1.170	100.12±0.109
F10	4.68±0080	5.32±0.121	0.34±0.021	500.6±0.932	100.12±0.186
F11	4.77±0.085	5.13±0.149	0.33±0.017	500.5±1.080	100.23±0.122
F12	4.69±0.067	5.05±0.150	0.37±0.026	499.9±0.534	100.16±0.170

Number of experiments n=3, mean±SD

where HPMC contributed as the floating matrix, MCC to increase the bulk density of the tablet and sodium bicarbonate to initiate the dissolution process.[14] The results were tabulated in table 5.

In Vitro Dissolution Studies of Prepared Tablets

The *in vitro* dissolution studies were conducted for all formulations in triplicate and the dissolution graph was drawn with error bars pertaining to the standard deviation of the three tests. All tablets retained their integrity throughout the study and released the drug in a controlled manner as shown in the Figure 1. Eight batches of formulations (F1-F8) which had HPMC composition up to 140 mg had an earlier release of drug for the same amount of sodium bicarbonate. In this, F7 had the longest floating time of 8 h. In the remaining four batches of formulations, F10 got completely dissolved at 10.5 h but the other three batches of F9, F11 and F12 showed floating time larger than 12 h.[15] The disadvantage of the Ayurvedic formulation is the drug stability and most of the plant-based drugs are delivered in the form of film coated tablet, which has the dissolution of 97.6% at 45 min and to overcome this issue a new technique is required. Thus from the results obtained, it was found that the bioavailability of the drug has been enhanced compared to that of the film coated tablets.

Release Kinetics

The various kinetic models were analyzed for all the formulations. It was found from the Table 6 that the optimum formulation was

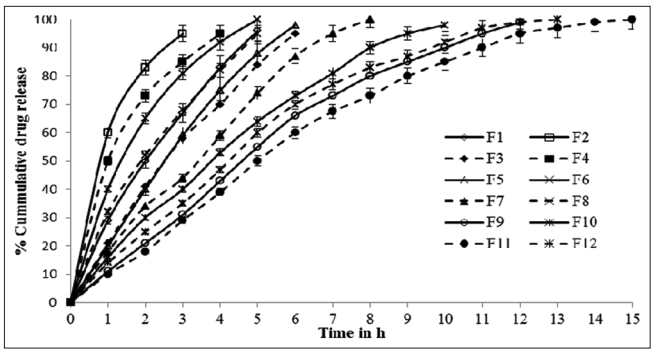

Figure 1: In vitro dissolution profiles for different formulations

Table 5: Result of floating property of herbal tablet

Formulation code	*Floating lag time (s)*	*Total floating duration (h)*
F1	44	5.5
F2	55	3.5
F3	50	6.5
F4	52	4.5
F5	45	6.5
F6	40	5
F7	39	8
F8	42	5.5
F9	37	12.5
F10	40	10.5
F11	35	15
F12	39	12.5

Number of experiments n=3, mean

Table 6: Dissolution kinetics analysis

Formulation Code	Zero Order		First Order		Highuchi		Korsmeyer Peppas		
	K0	R2	K1	R2	KH	R2	KK	n	R2
F1	20.37	0.9503	0.2462	0.8066	39.88	0.9503	1.4732	1.4661	0.9975
F2	34.82	0.6971	0.4673	0.9266	56.53	0.9879	1.7914	0.7975	0.9843
F3	16.83	0.9705	0.1937	0.7805	35.53	0.9283	1.3451	1.6621	0.9941
F4	26.69	0.7575	0.3376	0.8930	48.49	0.9853	1.7119	0.9038	0.9912
F5	17.33	0.9712	0.2195	0.8098	36.52	0.9163	1.3272	1.7576	0.9901
F6	23.92	0.8312	0.3087	0.8945	45.40	0.9814	1.6311	1.1163	0.9831
F7	13.95	0.9782	0.1768	0.7719	32.45	0.9095	1.2616	1.6978	0.9954
F8	20.35	0.9331	0.2408	0.7998	39.96	0.9625	1.5051	1.3551	0.9987
F9	9.12	0.9549	0.1126	0.8156	26.68	0.9101	1.0591	1.8220	0.9854
F10	11.03	0.9421	0.1350	0.8499	29.52	0.9398	1.2377	1.5679	0.9937
F11	7.97	0.9276	0.1069	0.8377	25.42	0.9255	1.0492	1.7385	0.9819
F12	9.30	0.8997	0.1267	0.8443	27.76	0.9419	1.1744	1.5982	0.9798

Number of experiments n=3, mean)

F11 i.e. having HPMC K4M had the minimum floating lag time and higher drug release. The optimized formulation F11 was found to follow typical Korsmeyer and Peppas model, which clearly indicated by their relatively higher R2 value of 0.9819 compared to the zero order, first order regression coefficient values and Higuchi diffusion model. The entire exponent 'n' values were found to be greater than 1 indicating that all the formulations were following Case II transport. Also, the rate constant KK and n were 1.0492 and 1.7385 with a significance of $P<0.05$.[16]

Antidiabetic Study of Different Formulations

Effect on Blood glucose level

The induction of diabetes with streptozotocin increases the blood glucose level significantly ($p<0.001$) in group II rats as compared to normal rats. In 21 day study glibenclamide the standard drug restored the blood glucose highly significantly with the $p<0.001$ in 14 days decrease in glucose levels.[17] The results were expressed in table 7.

Conclusion

Thus it was taken as the optimum formulation. Hence stability studies were carried out on F11 and there was a marginal increase of moisture content and hardness, while no change in the friability was found, showing that these changes were within the specified limits. The effect of ingredients in the polyherbal tablet was analyzed, where HPMC contributed as the floating matrix, MCC to increase the bulk density of the tablet and sodium bicarbonate to initiate the dissolution process.

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