Original Article

DEVELOPMENT OF BILAYER TABLETS FOR IMMEDIATE AND CONTROLLED RELEASE OF ALLICIN

MANOJ KR. DAS[1*], BHANU P. SAHU[1], JAHAN NUR RAHMAN HAZARIKA[1]

Girijananda Chowdhury Institute of Pharmaceutical Science (GIPS), Hatkhowapara, Azara, Guwahati 781017 Assam
Email: mdas5416@gmail.com

ABSTRACT

Objective: The purpose of this study was to develop and evaluate bilayer tablet for the immediate and controlled release of Allicin (Garlic Extract) for effective treatment of Hypertension.

Methods: The immediate release layer was prepared by using super disintegrants-sodium starch glycolate and binder used xantham gum and the sustained release layer was prepared by using hydrophilic polymer like HPMC K 100 and PVP. Before preparation of the tablets, all the pre-formulation parameters were checked and the tablet of Allicin were prepared by direct compression method and was evaluated for physical characteristics like hardness, weight variation, drug content and friability. *In vitro* release of drug was performed USP type II dissolution test apparatus using phosphate buffer (pH 7.4) as dissolution media and dissolution was continued for 8 hrs for the sustained release layer.

Results: It was found that all the formulations were within the limit of the standard. The drug release of the tablet was in the range of 66%-83% in 8 h.

Conclusion: It was concluded that the F4 formulation showed the optimum result as a bilayer tablet for the effective treatment of hypertension.

Keywords: Bi layer tablet, Allicin, Superdisintegrants, Polymer, Direct compression, *In vitro* dissolution study

INTRODUCTION

The oral route is the most promising and convenient route of drug administration. Conventional immediate release system achieves as well as maintains the drug concentration within the therapeutically effective range, but one has to take such formulations several times a day [1]. This results in significant fluctuations in plasma drug levels and also the frequency of administration leads to patient non-compliance. Recently, several technical advancements in the pharmaceutical field have led to the development of many novel drug delivery systems that could revolutionise the method of medication and provide a number of therapeutic benefits [2]. Systems can include the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance [3] While these advantages can be significant, the potential disadvantages cannot be ignored like the possible toxicity or non-biocompatibility of the materials used, undesirable by-products of degradation, any surgery required to implant or remove the system, the chance of patient discomfort from the delivery device, and the higher cost of controlled-release systems compared with traditional pharmaceutical formulations [4].

Several pharmaceutical companies are currently developing bi-layer tablets, for a variety of reasons: patent extension, increment in therapeutic efficacy etc. Bi-layer tablet is a new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system and it is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose.[5] Bi-layer tablets can be primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles. The present article provides a review on the oral drug delivery system, types of tablets, Bilayer tablet manufacturing, various tablet presses used, quality and GMP requirements for high production output and recent developments in the field of Bilayer technology and why development and production of quality bi-layer tablets need to be carried out on purpose built tablet presses, such as layer separation, insufficient hardness, inaccurate individual layer weight control, cross contamination between the layers, reduced yield [6].

Allicin is an organosulphur compound, obtained from garlic. The aroma of garlic when freshly crushed is because of the content allicin released by the action of the enzyme allinase on the substrate alliin [7]. Allicin is an oily based yellowish liquid, which gives garlic its unique colour. Its biological activity can be attributed to both its antioxidant activity and its reaction with thiol containing proteins. The content of garlic by whole weight to its concentration of the bioactive compound is 1:0.001. Allicin has a very short half-life. Alliinase is irreversibly deactivated below pH 3; as such, allicin is generally not produced in the body from the consumption of fresh or powdered garlic [8]. Allicin is unstable, breaking down into inactive components at 23 0 C, thus cooking destroys the bioactive component of garlic. Allicin exhibits lipid lowering, blood thinner, increases local circulation and platelet inhibitor action thus preventing aggregation and clot formation [9].

The aim of the present work is to formulate and evaluate bilayer tablet of Alicin for controlled antihypertensive effect and to achieve immediate release and sustained release of Alicin using bilayered tablet [10].

MATERIALS AND METHODS

Materials

Allicin was obtained from Ayurbedic college, Guwahati, assam; Dicalcium Phosphate, Microcrystalline Cellulose, Xanthum gum, Sodium Starch Glycolate, Cross Carmellose Sodium, HPMC K 100, PVP, Magnesium Stearate, Talc were obtained from Merk Specialist pvt. Ltd., Mumbai-18. All other chemicals used were of analytical grade.

Methodology

Physico chemical parameters

Solubility determination [1]

A minute quantity of the drug sample was taken in a test tube and solubility of the drug dissolving in 1 ml of various solvents

like water, methanol, ethanol, phosphate buffer etc was observed.

Estimation of allicine in analytical sample

Preparation of standard calibration curve of Allicin in phosphate buffer pH 7.4 [3]

100 mg of drug allicin was weighed accurately and dissolved in 100 ml of phosphate buffer in 100 ml volumetric flask (stock solution). 10 ml was taken from the stock solution and transferred into 100 ml volumetric flask and diluted up to 100 ml with phosphate buffer. From above standard working solution 1 ml, 2 ml, 4 ml, 6 ml, 8 ml, 10 ml up to 20 ml was withdrawn and diluted up to 10 ml Phosphate buffer in 10 ml volumetric flask to get concentration of 20 µg/ml, 40 µg/ml, 60 µg/ml, 80 µg/ml, 100 µg/ml respectively. The absorbance

of each solution was measured by UV-visible spectrophotometer at 247 nm using phosphate buffer as blank.

Formulation of tablet [4]

The immediate release layer was prepared by using super disintegrants-sodium starch glycolate and xantham gum as a binder and the sustained release layer was prepared by using hydrophilic polymer like HPMC K 100 and PVP. The various ratios of the ingredients used are shown in the formulation table, table 1 before preparation of the tablets all the pre-formulation parameters was checked and the drug and excipients were mixed using suitable blenders to get a premix for direct compression into tablets. And the mixture was then evaluated for various pre-compression parameters such as Bulk Density, Tapped Density, Angle of repose, Hausner's Ratio, Carr's Index.

Table 1: Formulation of bilayer tablets

Immediate release layer						
Ingredients	F1	F2	F3	F4	F5	F6
Drug (mg)	20	20	20	20	20	20
Talk	2	2	2	2	2	2
Mg stearate	2	2	2	2	2	2
Xantham gum	5	5	5	5	5	5
SSG	12	12	12	12	12	12
Dicalcium Phosphate	39	39	39	39	39	39
MCC	39	39	39	39	39	39
Sustain release layer						
Drug	30	30	30	30	30	30
PVP	0	0	10	20	6	14
HPMC	10	20	0	0	0	0
Talk	4	4	4	4	4	4
Mg stearate	4	4	4	4	4	4
Xantham gum	20	20	20	20	20	20
MCC	132	132	132	132	132	132

Pre-compression parameters

Bulk density (D_b) [5]

The accurately weighed powder was carefully transferred into the graduated measuring cylinder. The power bed was then made uniform and the volume occupied by the powder was noted as per the graduation marks on the cylinder as ml. It is expressed in gm/ml and is calculated using the following formula.

$$D_b = M/V_b$$

Where, M-Mass of the powder

V_b-Bulk volume of the powder

Tapped density (D_t) [5]

It is the ratio of total mass of powder to the tapped volume of powder. The graduated measuring cylinder containing accurately weighed powder was manually tapped for 50 times. Volume occupied by the powder was noted. It is expressed in gm/ml and is calculated by following formula.

$$D_t = M/V_t$$

Where, M-Mass of the powder

V_t-Tapped volume of the powder

Angle of repose (θ) [5]

The frictional forces in a loose powder can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Sufficient quantities of Allicin powder were passed through a funnel from a particular height (2 cm) onto a flat surface until it formed a heap, which touched the tip of the funnel. The height and radius of the heap were measured. The angle of repose was calculated using the formula.

Angle of repose (θ) = tan-1 (h/r)

Where, h–Height of the pile in cm

r–Radius of the pile.

Compressibility index (I) and Hausner's ratio [5]

Carr's index and Hausner"s ratio measure the propensity of powder to be compressed and the flowability of granule. Carr"s index and Hausner"s ratio were calculated using following formula.

$$I = Dt–Db/Dt × 100$$

Where, Dt–Tapped density of the powder

Db–Bulk density of the powder

Hausner"s ratio= Dt/Db= Vb/Vt

Compression of Bilayer tablets [6]

The bilayer tablets of Allicin were prepared by direct compression method and were evaluated for post compression physical characteristics like hardness, weight variation, drug content and friability. *In vitro* release of drug was performed USP type II dissolution test apparatus using phosphate buffer (pH 7.4) as dissolution media and dissolution was continued for 8 h for the sustained release layer.

Post compression parameters

Tablet dimensions [10]

Thickness and diameter were measured using calibrated digital Vernier callipers. Five tablets of each formulation were picked randomly and thickness and diameter was measured individually

Hardness test [11]

The prepared tablets were subjected to hardness test. It was carried out by using Monsanto hardness tester and expressed in kg/cm².

Friability test [11]

Tablet friability was tested by Roche friabilator. Pre weighed tablets were given 100 revolutions in 4 min and were dedusted. The percentage weight loss was calculated by reweighing the tablets.

$$\%F = \frac{[W\ (initial) - W\ (final)]}{[W\ (initial)]}\ x\ 100$$

Weight variation test [11]

20 tablets were selected at random from the lot, weighed individually and the average weight was determined. The percent deviation of each tablets weight against the average weight was calculated. The test requirements are met, if not more than two of the individual weights deviate from the average weight by more than 5% and none deviates more than 10%.

Drug content study [12]

Three tablets were weight and average weight was determined and powdered. 320 mg of powder was accurately weight and transferred into a 100 ml volumetric flask. It was dissolved and made up the volume with phosphate buffer pH7.4. After that 1 ml solution diluted in 10 ml phosphate buffer solution. And analyzed at 247 nm using UV-Visible spectrophotometer. The drug content of each sample was estimated from standard curve of Allicin in phosphate buffer pH7.4.

Drug release study [12, 13]

Drug release studies of formulated tablets were conducted in the USP (II) dissolution test apparatus (Lab India, DS8000) using phosphate buffer pH7.4 as dissolution medium maintained at 37. 2 ° C. The dissolution vessels were filled with 900 ml of phosphate buffer pH7.4. The vessel maintained at 50 rpm under stirring conditions by means of paddle fabricated for purpose in dissolution apparatus.

The drug dissolution was studied up to 8 h using U. V spectro-photometry at 247 nm.

Drug release kinetics [13]

Zero order

To study the Zero–order release kinetics the release rate data are fitted to the following equation.

$$F = K.\ t$$

Where,

F is the fraction of drug release,

K is the release rate constant, and t is the release time.

RESULTS AND DISCUSSION

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys Zero-order release kinetics, with a slope equal to K.

Higuchi's model

To study the Higuchi kinetics the release rate data are fitted to the following equation-

$$Q = K_H\ t^{1/2}$$

Where Q is the amount of drug release at time t, and K_H is the Higuchi rate constant.

Hixson–Crowell model

The release rate data were fitted to the following equation-

$$Q0^{1/3} - Qt^{1/3} = KHC\ t$$

Qt is the amount of drug released in time t, Q0 is the initial amount of the drug in tablet and KHC is the rate constant

Korsemeyer-peppas release model

$$M_t/M\infty = kt^n$$

Where M_t is the amount of drug release at time t and M∞ is the amount of drug release after infinite time, M_t/M^{∞} is the factional drug release % at time t, K is a constant related to the properties of the drug delivery system and n is the release exponent indicative of the drug release mechanism.

Drug-excipients compatibility study

FT-Infrared spectroscopy study [13]

The FTIR analysis was carried out of the pure drug, excipients and the formulation to evaluate the physical stability and compatibility of the drug with the excipients. 10 mg of the sample were taken in a mortar and triturated. A small amount of the triturated sample was taken onto the sample holder and scanned from 400 cm^{-1} to 4000 cm^{-1} in FT-IR spectrophotometer (Bruker Alpha-E, modedl no-10059736). The spectra obtained were compared and interpreted for the functional group peaks.

Differential scanning calorimetry study [13]

A Differential scanning calorimeter (Perkin Elmer (USA), Model-jade DSC) was used for determining the compatibility of drug and the excipients. Individual sample of pure drug, excipients and the formulation were weighed to about 5 mg in the DSC aluminum pan and scanned in the temperature range of 50-300 ° C in nitrogen environment. A heating rate of 10 °C per minute was used, and the thermo gram were reviewed for evidence of any interaction.

Table 2: Pre formulation studies of the drug

S. No.	Parameters	Result
1	Organoleptic Properties	
	Bulk Characteristic	Crystalline powder
	Color	Light Brownish red
	Odor	Characteristic
2	Solubility	Partially insoluble in water
		Freely soluble in methanol
		Soluble in alcohol
3	Absorption spectra	247 nm

Table 3: Pre-formulation studies of the powder

Formulation code	Bulk density gm/ml	Tapped density gm/ml	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
F1	0.552	0.503	7.32	1.1	25.5
F2	0.573	0.513	6.45	1.17	23.33
F3	0.535	0.495	9.52	1.15	27.34
F4	0.582	0.552	7.57	1.19	25.32
F5	0.522	0.531	8.51	1.14	24.42
F6	0.594	0.556	9.53	1.15	25.57

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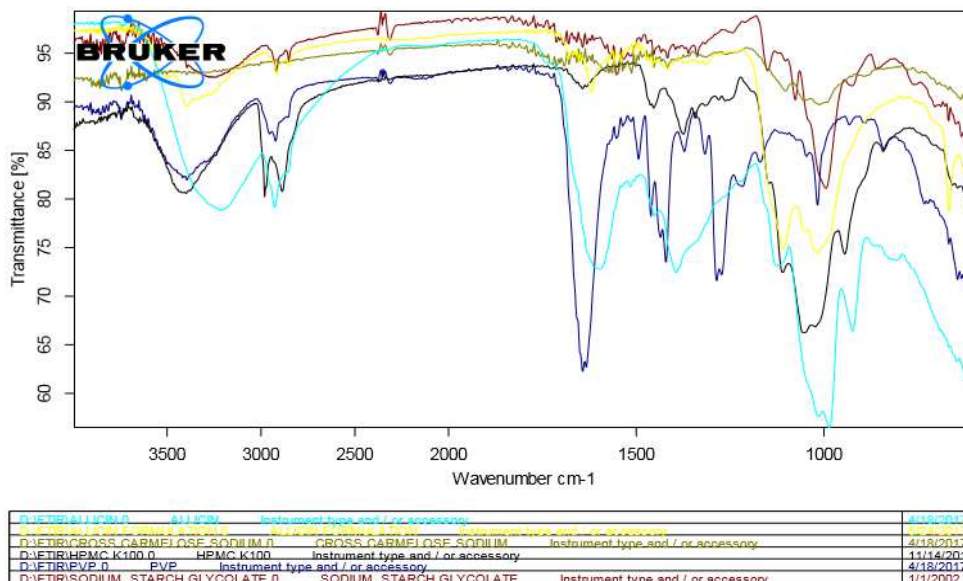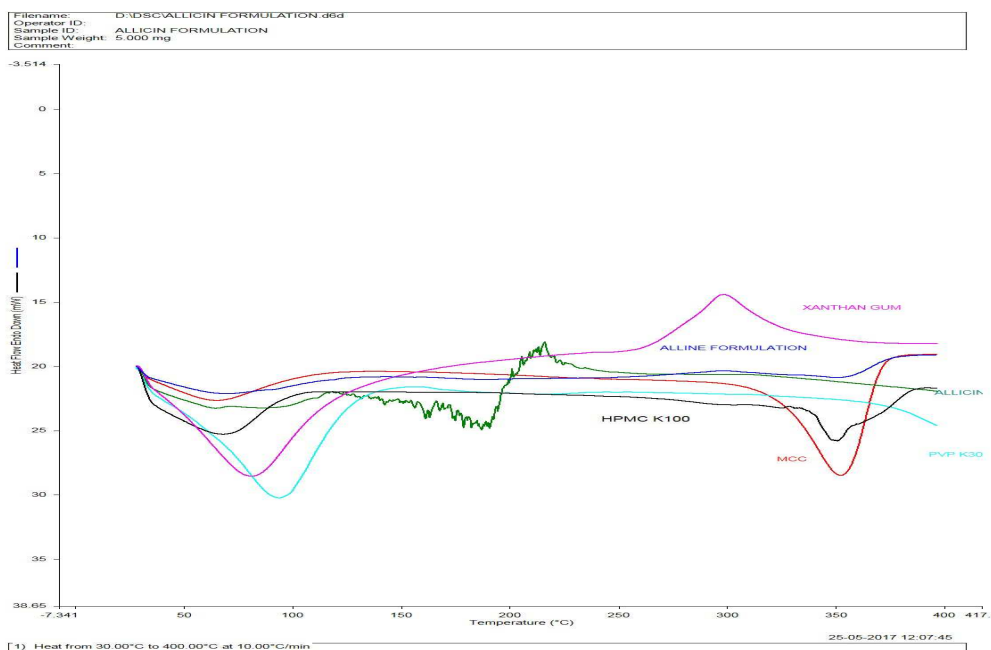Guwahati, Assam

Fig. 1: FTIR of drug and excipients

Fig. 2: DSC thermogram of drug, excipients and formulation. (SSG-sodium starch glycolate, CCS, MCC-micro crystalline cellulose)

Table 4: Post compression parameters

Batch code	Wt. variation %	Hardness (kg/cm²)	Thickness (mm)	Drug content %
F1	318±2.20	3.6	4	97.45
F2	315±3.1	3.8	4	102.91
F3	321±1.2	4.2	3.8	93.23
F4	318±2.2	4.3	4.1	96.37
F5	316±2.8	3.8	4.1	95.37
F5	321±1.2	4.5	3.8	98.41

Fig. 3: Calibration curve of allicine in phosphate buffer pH 7.4

Table 5: Dissolution results

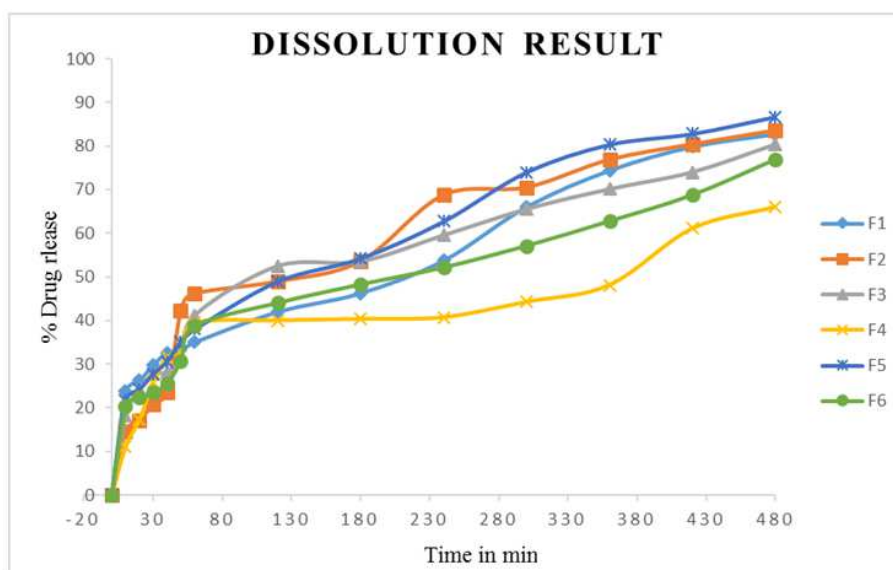| Time	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
10	23.705882	14.647059	18.176471	11.117647	21.705882	20.364706
20	26.247059	17.188235	24.247059	17.258824	24.247059	22.411765
30	29.776471	20.717647	27.776471	25.835294	27.776471	23.541176
40	32.6	23.541176	28.129412	31.552941	30.6	25.588235
50	33.188235	42.247059	31.658824	32.752941	35.188235	30.776471
60	35.011765	46.129412	41.188235	39.423529	38.011765	38.717647
120	41.952941	48.952941	52.482353	40.058824	48.952941	44.011765
180	46.247059	53.541176	53.541176	40.376471	54.247059	48.247059
240	53.717647	68.717647	59.541176	40.764706	62.717647	52.129412
300	66.011765	70.482353	65.541176	44.294118	74.011765	57.070588
360	74.364706	76.835294	70.129412	48.141176	80.364706	62.717647
420	79.835294	80.364706	74.011765	61.094118	82.835294	68.717647
480	82.717647	83.541176	80.364706	66.035294	86.717647	76.835294

Fig. 4: Dissolution curve

Table 6: Release kinetics parameters

Formulation	Zero order R²	First Order R²	Higuchi R²	Hixon crowell R²	Korsemeyer-peppas (n)
F1	0.5101	0.7678	0.9451	0.7053	0.394
F2	0.5506	0.8684	0.9497	0.7991	0.420
F3	0.3966	0.7633	0.9395	0.6685	0.370
F4	0.1246	0.3822	0.7916	0.3007	0.313
F5	0.5419	0.8589	0.9719	0.7930	0.404
F6	0.4118	0.6987	0.9395	0.6187	0.371

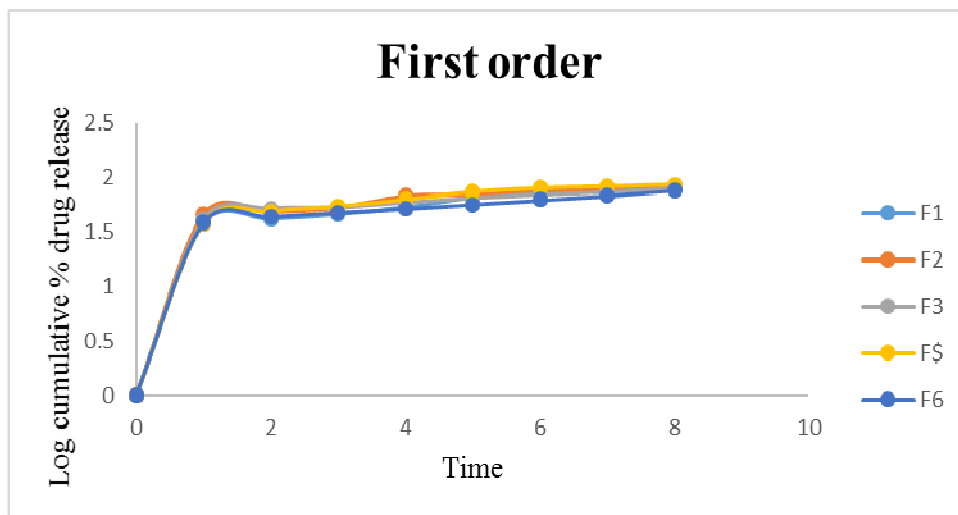Fig. 5: Plot showing zero order kinetics of 6 formulation

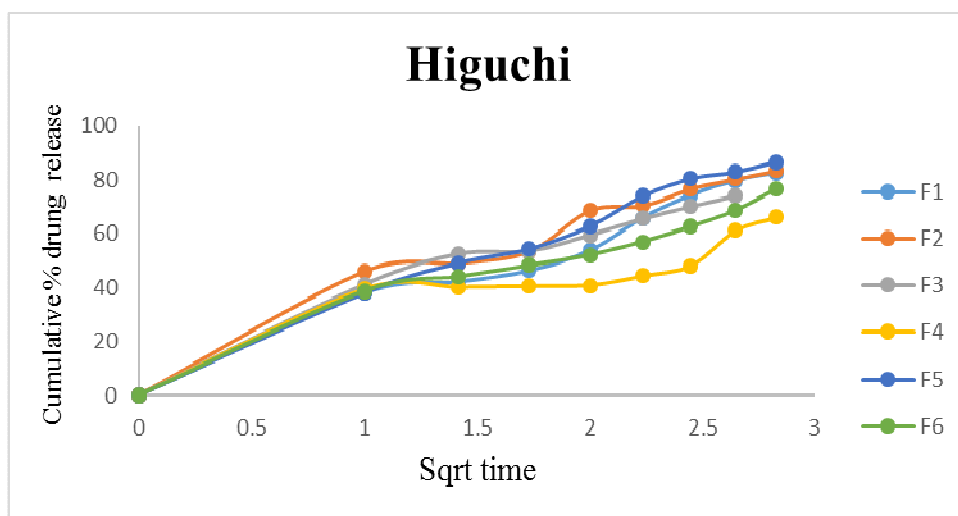Fig. 6: Plot showing first order kinetics of 6 formulation

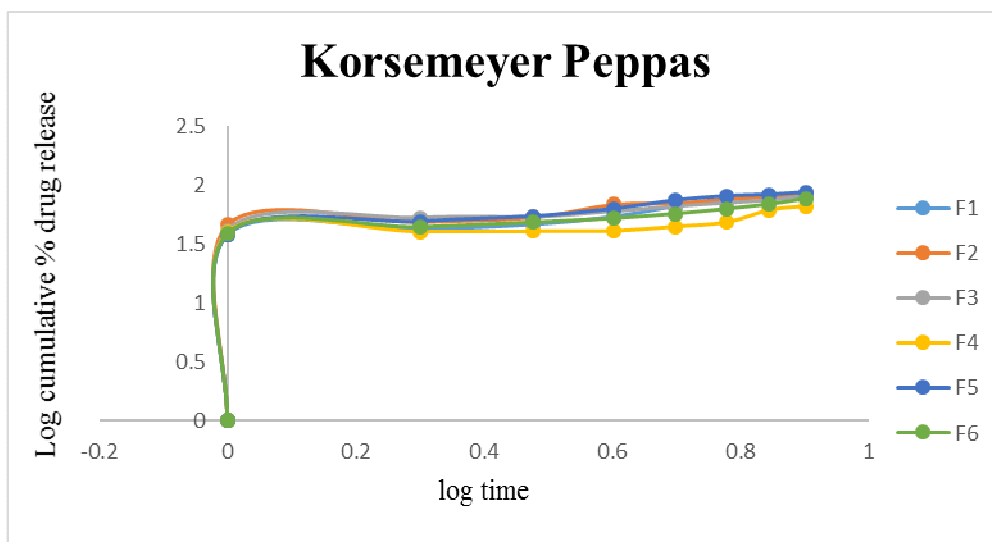Fig. 6: Plot showing higuchi model of 6 formulation

Fig. 7: Plot showing korsemeyer pappas model of 6 formulation

RESULTS AND DISCUSSION

The drug is soluble in Alcohol, partially soluble in water, freely soluble in methanol and phosphate buffer. The characteristic of the drug is polar. The bulk characteristic of the drug is crystalline, color obtain light brownish red and odor characteristic. The prepared Allicin powders for tableting were prepared by the suitable blender. The prepared powder were evaluated for angle of repose, bulk density, tapped density and compressibility index, Hausner's ratio. The bulk densities and tapped densities of the powder were found to be in the range of 0.522 to 0.594 gm/ml and 0.495 to 0.503 gm/ml. The angle of repose varied from 23.33 to 25.57 which indicate good flow properties of the powder. Hausner's ratio was ranged between1.1 to 1.19, while the compressibility index was in the range of 6.24 to 9.53 these values indicates that the powder mixture of all batches of formulation exhibited good flow properties.

The prepared tablets were evaluated for Weight variation, Hardness, Friability, Thickness, drug content. Thickness was found to be in the range of 3.8 to 4.1 mm and the hardness of the tablets was in the range of 3.6 to 4.8 kg/cm2 which was sufficient for the handling of tablets throughout the shelf life. % friability was between 0.67–0.96 % which is within the acceptable limit. From the weight variation test the % weight variation for all 20 tablets were found 321±1.2-315±3.1 in and the drug content was found to satisfactory in the range of 93.23-102.91%. Drug and excipient are accurately weight and compress by direct compression method using 6 mm dye. Six formulation are done properly. The *in vitro* dissolution studies were carried out for all the 6 formulation in USP apparatus type II using dissolution medium of phosphate buffer pH 7.4. The percentage release of Alicin tablet are plotted. Above this 6 formulation, the formulation F4 with the concentration of polymer PVP 20 mg showed better drug release by releasing 66% at the end of 8 h. From the kinetic study the drug release from drug layer follows Higuchi equation. And from the Korsemeyer-Peppas model the "n" values of the prepared formulation were found to be between 0.313 to 0.4109 (<0.5) indicating diffusion controlled release of drug.

The FT-IR was performed for drug, excipients and tablet Formulation. From the FT-IR study it is clearly understood the identical FT-IR bands were also present in the drug excipients physical mixture as like that of the drug. This confirms that there are no drug excipient interactions present. DSC studies of the pure drug and excipient were carried out to determine if there was any interaction between the drug and the excipient. The spectra showed peak at 156.14 °C for the drug itself and at 71.70 °C for the mixture which corresponds to its melting point. Thus, the thermal data did not reveal any interaction between the drug and the excipients used for the prototype formulation development.

CONCLUSION

The present work involves the bi layer tablets for the immediate and controlled release of Allicin using HPMC K100 and PVP as a retardant polymer. The drug-excipient compatibility studies confirmed that the both drugs are compatible with selected polymer HPMC K100 and PVP. The pre-compression parameters and post compression parameters were obtained from both the layers and were within the acceptable limits. The drug release study from Allicin sustains release layer showed that as the concentration of the polymer increase the drug release is decreases. The release of drug in the first hour varies between 35.01 to 46.12 and the second layer duration of drug release varies 66.03 to 86.71. The results reveal that with increase concentration of HPMC K100 and PVP retardation of drug release takes place. From the kinetic study the drug release from drug layer follows Higuchi equation and Korsemeyer-Peppas indication drug release. The "n" values of the prepared formulation were found to be between 0.313 to 0.4109 indicating diffusion controlled release of drug. The drug release study tablet showed desired release profile for both layer. The complete drug release is taken eight hours. Hence the formulated bi layer tablet can be used for effective and prolonged management of Blood pressure and it use for the treatment of Hypertension.

CONFLICT OF INTERESTS

Declare none

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