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FORMULATION DEVELOPMENT AND EVALUATION OF DOXOPHYLLINE HYDROCHLORIDE FLOATING TABLETS

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ABSTRACT

Sustained release gastro retentive dosage forms enable prolonged and continuous input of the drug to the upper parts of the gastrointestinal tract and improve the bioavailability of medication. The study was carried out with an objective to achieve a potential sustained release oral drug delivery system of an antiasthmatic drug, Doxophylline which is a bronchodilator xanthine drug which has the therapeutic properties similar to theophylline with lower incidence of side-effects & having half life of 6 hours. As the Doxophylline is water soluble drug, can control or delay the release rate of drug by using release-retarding polymers. This may also decrease the toxic side effects by preventing the high initial concentration in the blood. Floating tablets were prepared by wet granulation method using various release retarding polymers like HPMCK100M, HPMC K4M, carbopol 934P, PVPK30, Sodiumbicarbonate, citricacid magnesium stearate and talc in combination were tried and optimized to get the release of 14 hr. Prepared floating tablets were prepared for floating properties, swelling characteristics and *In vitro* release studies.. Infrared spectroscopy (IR) study and differential scanning calorimetry (DSC) study show that drug and other excipients are compatible with each other. The floating tablets were stored at temperature of 40°C ± 2°C/75% ± 5% RH were unchanged during 2 months of storage condition. Hence from the result we can conclude that Doxophylline floating tablets can be successfully designed to develop sustained drug delivery, that reduces the dosing frequency and their by one can increase the patient compliance.

INTRODUCTION

Floating drug delivery systems (FDDS) have bulk density lesser than gastric fluids, so they remain buoyant in the stomach.

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Without affecting the gastric emptying rate for a prolonged period. The FDDS can be retained in the stomach and assists in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the GIT. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug

waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.[7].A minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature.

MATERIALS AND METHODS

Doxofylline is gifted from Burgeon Pharmaceuticals, chennai, carbopol is purchased from Yarrow Chem Products, Mumbai. Sodium bicarbonate is from Nice Chemicals Pvt Ltd , Kerala. HPMC K100M and HPMC K15M was purchased from Yarrow Chem Products. Magnesium Stearate procured from Loba Chemicals.

Preparation of Doxofylline hydrochloride floating tablet by wet granulation method.

All the materials were weighed accurately according to formula. Shift the material through 80 no. mesh except magnesium stearate and talc. Mix the drug polymer and citric acid by geometrical mixing in a double polybag for 10 min. Above mixed material add sodium bicarbonate as a gas generating agent.

Again mixed for 5 min. The mixture was granulated using) PVP K30 (polyvinyl pyrrolidon) dissolved in sufficient isopropyl alcohol by passing through sieve no.12. Granules were dried at 45°C for 4 h. The dried granules were passed through sieve no 20. To the dried granules magnesium stearate and talc were added and it is further mixed in a double cone blender . Tablets were compressed on a 10 station mini tablet press using 16/32 sized punch with flat surface and round shape.

Evaluation of blend:

Angle of Repose:

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose for the granules of each formulation was determined by the funnel method. The angle of repose was calculated by substituting the values of the base radius 'R' and pile height 'H' in the following equation

Tan $\underline{\emptyset}$ = h/r

Flow Rate:

Flow rate of a powder has been defined as the rate at which the particular mass emerges through the orifice of funnel of a suitable diameter. The flow rate for granules of each formulation was determined by pouring accurately weighed quantities of granules in funnel with an orifice of 8 mm diameter. The time required for the complete granule mass to emerge out of the orifice was recorded using a stopwatch. The flow rate was calculated from following equation:

Flow Rate = Weight of granules/ Time in seconds

Polymer Swelling or Water Uptake Studies:

The individual tablet were weighed accurately and kept in 50 ml water. Tablets were taken out carefully after 60 min blotted with filter paper to remove the water present on the surface and weighed accurately. Percentage swelling index (SI) was calculated by using the formula,

SI=Wet weight –Dry weight/ Dry weight X 100

Floating Behavior:

The *In-vitro* buoyancy was determined by floating lag time. As per the method described by ***Rosa et. al*** the tablets were placed in a 100 ml beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface & float was determined as floating lag time.

Dissolution Studies

The *In vitro* dissolution studies of FDDS of Doxofylline were carried out in USPXXIII type 2 dissolution test apparatus, employing a paddle stirrer at 50 rpm using 900 ml of 0.1 N Hcl as dissolution medium. At predetermined time intervals, 10 ml of the samples were withdrawn by means of a syringe fitted with a pre filter. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium maintained at 37± 0.5^0C. The samples are analyzed for drug release by measuring the absorbance at 274 nm using UV/Visible double beam spectrophotometer after suitable dilutions.

Stability study:

The ICH Guidelines have established that long term stability testing should be done at 30^0C/60 % RH; stress testing should be done at 40^0C/75%RH for 6 months.

Table No: 1 Dosage form of FDDS with Examples of Various Drugs

S.no	Dosage Form	Drugs
1	Floating tablets	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin
2	Floating capsules	Furosemide, L-DOPA, Benserazide, Nicardipine
3	Floating microspheres	Aspirin, Griseofulvin, p-nitro aniline
4	Floating granules	Cinnarizine, Diclofenac sodium Diltiazem, indomethacin
5	Powders	Several basic drugs-Riboflavin,phosphate, Sotalol, Theophylline.

Table: 2 Formula for doxofylline floating tablet

FC	DRUG	HPMC K100M	HPMC K4M	CARBOPOL 934P	PVP	Citric acid	$NaHO_3$	Talc	Magnesium stearate
F1	400	-	100	-	30	50	90	5	5
F2	400	-	85	20	30	50	85	5	5
F3	400	-	-	100	30	50	90	5	5
F4	400	60	40	40	30	50	85	5	5
F5	400	60	-	50	30	50	80	5	5
F6	400	50	50	-	30	60	80	5	5
F7	400	100	-	-	30	55	85	5	5

Table: 3 Stability Protocol

Stability conditions		
$30^0\pm2^0$C/65±5%RH & $40^0\pm2^0$C/75±5%RH		
1Month	2 Month	3 Month

Table: 4-Results of Swelling Index Studies of Doxofylline Floating Tablets

FC	0	1	2	3	4	5	6	7	8	9	10	11	12
F1	0	20	30	41	54	63	70	76	81	89	-	-	-
F2	0	17	26	35	49	57	65	71	76	83	-	-	-
F3	0	12	25	34	39	45	59	68	75	84	88	-	-
F4	0	24	30	38	48	56	63	69	76	81	87	91	95
F5	0	20	29	38	46	54	67	73	79	85	88	89	-
F6	0	14	29	37	45	55	64	72	82	88	91	-	-
F7	0	15	24	34	41	49	64	69	76	82	-	-	

Table 5: Kinetic values obtained from different plots of formulation f4

FC	Zero order plot R^2	First order plot R^2	Higuchi's plot R^2	Kozmeyer pep-pa's plot R^2
F4	0.974	0.982	0.591	0.99

Table 6: *In vitro* dissolution studies

Time	F1	F2	F3	F4	F5	F6	F7
1	23.73	38.41	22.05	13.26	21.56	29.85	19.07
2	30.04	52.36	33.15	21.31	32.04	38.45	27.52
3	55.41	64.05	47.15	30.78	41.73	49.05	39.44
6	71.08	75.89	56.14	43.81	55.43	61.34	51.41
8	84.31	91.05	68.7	59.21	61.57	75.03	63.05
10	92.45	-	79.89	71.05	78.93	83	82.07
12	-	-	93.01	83.84	92.81	91.14	94.12
14	-	-	-	96.63	-	-	-

Table 7: Stability study parameters of formulation F4

Evaluation parameters	Initially	After 2 months
Weight variation (mg)	680±1.19	680±1.19
Hardness	6.0	6.0
% Friability	0.431	0.452
Floating lag time(sec)	45	45
Total floating time(hr)	>14	>14
In vitro dissolution Study (after 14 hr)	96.63%	96.45%

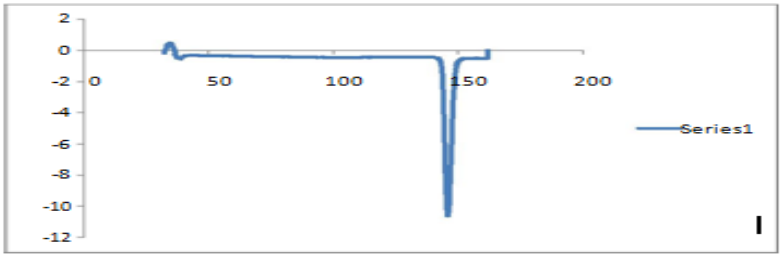


Fig :1- DSC Thermogram of Pure Doxophylline

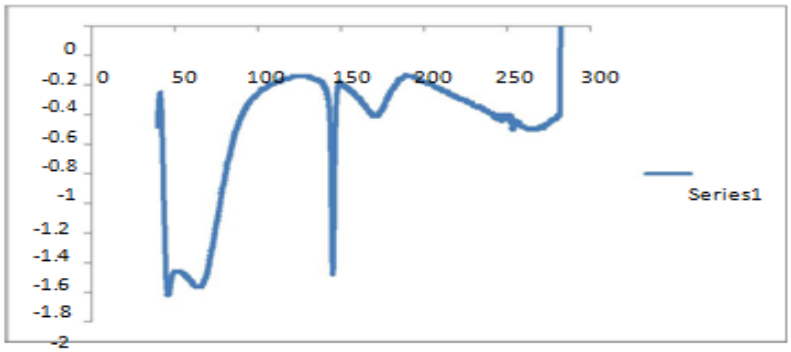


Fig 2: DSC Thermogram of Doxofylline +Polymeres

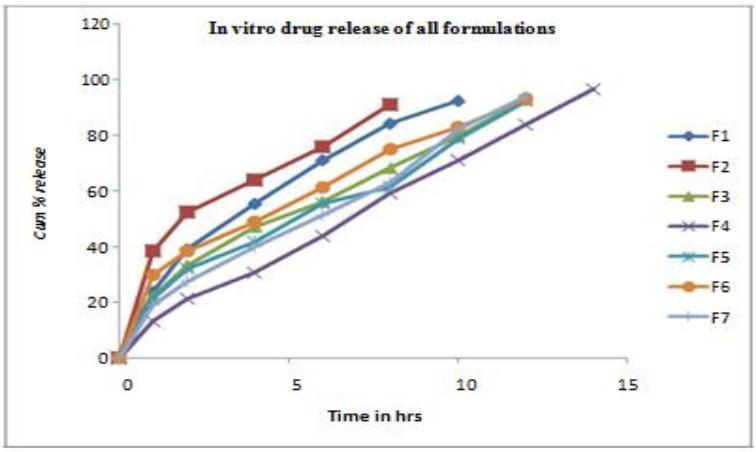


Fig:4- Zero order plot of formulation F4

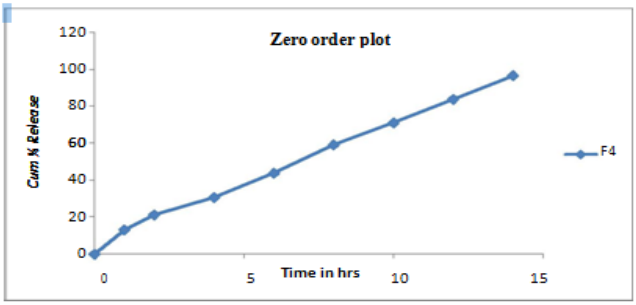


Fig:5 -First order plot of formulation F4

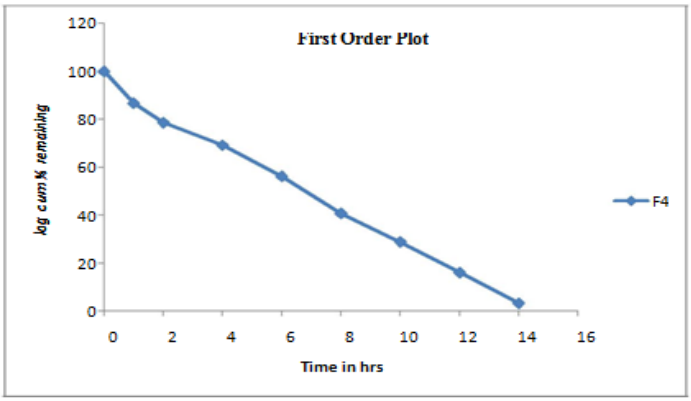
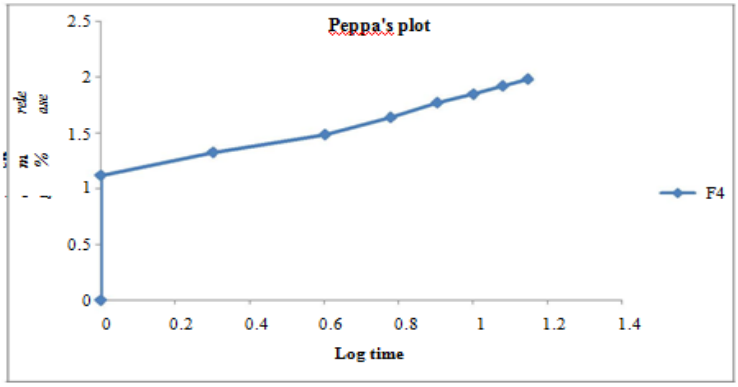


Fig :6- Peppa's model plot of formulation F4



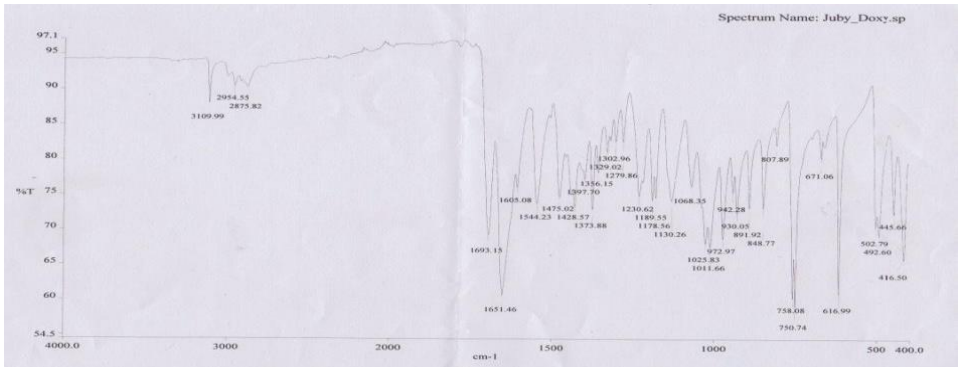


Fig:6- FTIR Spectra of Pure Doxophylline

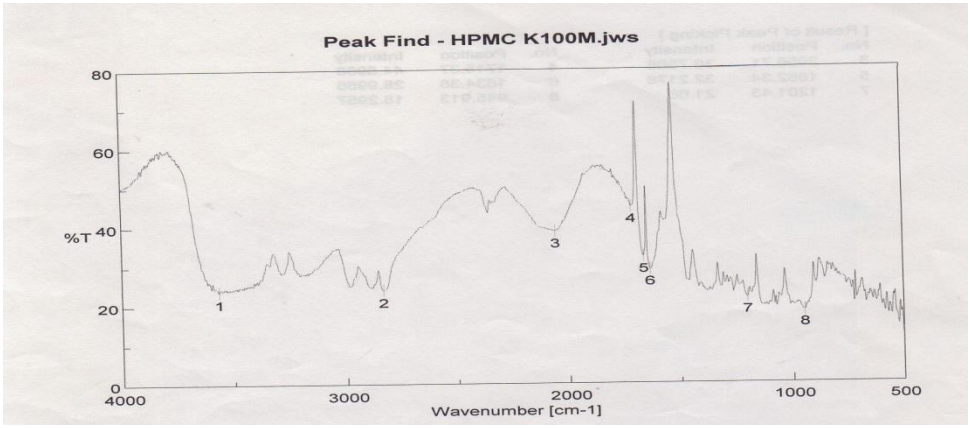


Fig:7- FTIR Spectra of HPMC K100M

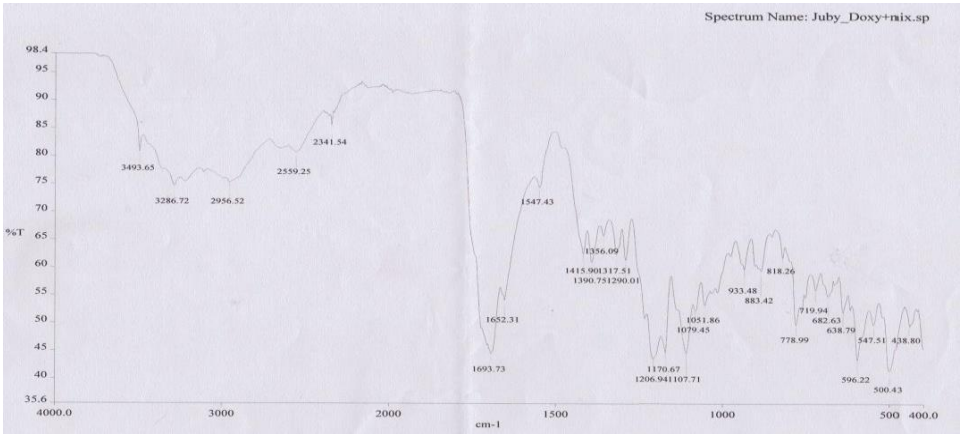


Fig: 8- FTIR Spectra of Doxophylline Mixtures

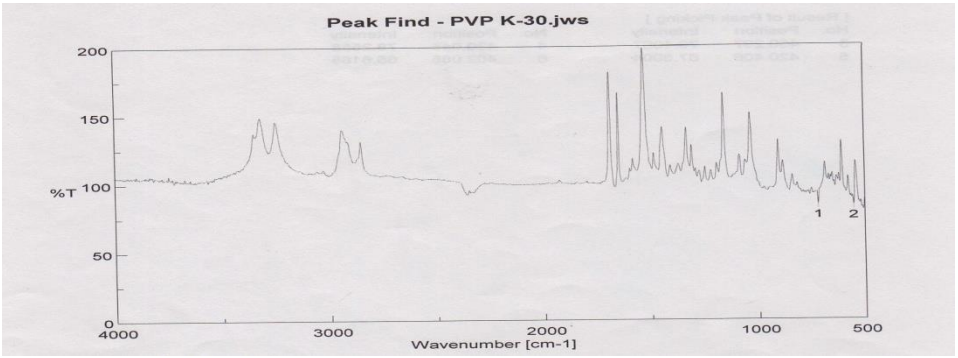


Fig 9: FTIR Spectra of PVPK30

If significant change occurs at these stress condition, then the formulation should be tested at an intermediate condition i.e 30^0C/75% RH. Table 5.6.1 shows different temperatures and period of stability testing. If 30°c±2°c/65% RH±5% RH is a long term condition there is no intermediate condition. In the present work, stability study was carried out for the optimized formulation F4 for following condition and time period.

RESULTS:

Assay of Doxophylline

Assay of Doxophylline was done by UV spectrophotometry method. The % purity of the drug was found to be 97.5%.

Differential Scanning Calorimetry (DSC):

Differential Scanning Calorimeter (DSC) allows the fast Evaluation of possible incompatibilities, because it shows changes in the appearance, Shift of melting endotherms and exotherms and/or variations in the corresponding enthalpies of reaction. The DSC thermograms of pure drug Doxophylline, other excipients and mixture were recorded.(Fig.) The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10°C/min over a temperature range of 50°C to 300°C.

Stability study of formulation (F4):

The optimized floating tablets (F4) were selected for stability study based on *in vitro* buoyancy and *in vitro* drug dissolution studies. The tablets were investigated at 40°C/75% RH for 2 months. From the data, the formulation is found to be stable under the conditions mentioned above since there was no significant change in the percentage amount of drug content (Table). Thus, it was found that the floating tablets of Doxofylline (F4) were stable under these storage conditions for at least 2 months.

DISCUSSION:

The purpose of the present study was to formulate floating tablets of Doxophylline Hydrochloride..Doxophylline is the antiasthmatic drug with half life of 6 hours. Therefore the study was done to combat the shorter half life of Doxophylline. The floating tablet was prepared by wet granulation method containing gas-forming agents, like sodium bicarbonate, citric acid and hydrocolloids. Method was developed for estimation of Doxophylline which showed maximum absorption at wavelength 274 nm and sodium phosphate buffer (pH 7.0). Beer's law was obeyed at concentration range of 1 µg/ml to 10 µg/ml and when subjected to regression analysis, the value of regression coefficient was found to be 0.9934, which showed linear relationship between concentration and absorbance. FTIR studies were carried out. IR spectrum for pure drug and physical mixture of drug- polymers were obtained and analyzed for principle peaks at 1693.7 cm^{-1} (C=O stretching), 1547 cm^{-1} (C=C), 778cm^{-1} (C-X), 1079cm^{-1} (C-N Vibration), 1652cm^{-1} (C=N), 2956.52 cm^{-1} (C-H stretching) .Spectra are shown in figures. DSC curves obtained for pure Doxophylline, HPMCK110M, HPMCK4M,Carbopol 934P,PVPK30, magnesium stearate and Talc and their physical mixtures are shown in the Fig.3 and 4. To obtain floating, the balance between swelling and water acceptance must be restored. The swelling index of floating tablets of F1 to F7 is shown in Table (4). Tablets containing Carbopol 934P (F3) showed less swelling index at the beginning but higher swelling index was observed at the end of 12 h. While HPMC K4M and HPMC K100M (F6,F7) swelled rapidly at the beginning in 0.1 N HCl. The combination of sodium bicarbonate and citric acid provided desired floating ability and therefore this combination was selected for the formulation of the floating tablets. The cumulative percentage of drug release as a function square root of time (Higuchi plot) was linear and it suggested that the release of Doxofylline, Carbopol 934P, HPMC K100M and HPMC K4M was diffusion controlled. The 'n' values obtained from the peppas-korsemeyer equation suggested that, all the formulation showed drug release by non-fickian diffusion mechanism.

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No research is ever the outcome of single individual's talent or efforts. I offer flowers of gratitude to the **almighty GOD** who has been the source of strength in my life. It is with great pleasure and profound sense of reverence that I express my gratitude and thanks to my esteemed guide **Mr. Ubaidulla U**, Assistant Professor, Department of Pharmaceutics, Shree Devi College of Pharmacy.

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