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FORMULATION AND EVALUATION OF FLOATING MATRIX TABLETS OF ONDANSETRON HYDROCHLORIDE

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ABSTRACT

***Aim**: The study is aimed to use water retarding kondagugu gum(Huppu gum) with sodium alginate for the development of floating matrix tablets of Ondansetron hydrochloride. **Methods:** Analytical methods, pre compression parameters, in-vitro drug release, buoyancy characteristics were determined for the formulations. It showed that retarding polymer had an impact on floating property. **Results and Discussions:** The formulation F2 is having maximum drug release and floating time i ,e 97.04 % release with zero order with higuchi diffusion mechanism up to 10 hours and floating lag time 34 sec. **Conclusion:** The drug release from developed formulations was found to be inversely proportional to kondagugu gum concentration.*

***KEYWORDS:** Ondansetron hydrochloride, Kondagugu Gum, Sodium alginate, Floating matrix tablets.*

INTRODUCTION

Floating formulations are prepared from hydrophilic matrices that either have a density lower than one or their density drops below one after immersion in the gastric fluids owing to swelling. Cellulose ether polymers are often used for formulation of floating matrices, and low-density fatty acids can be incorporated as well to decrease hydration rate and increase buoyancy. These forms are often called hydro dynamically balanced systems (HBS) as they can maintain low density and keep floating even after hydrating when a floating dosage form is administered with food; the device remains buoyant on the surface of the gastric contents in the upper part of the stomach and moves down toward the pyloric sphincter while the meal empties. The reported GRT of such floating devices varies from 4 to 10 hrs. The active drug is progressively released from the formulation matrix and thus introduced to the proximal intestine where it can be absorbed [1-10].

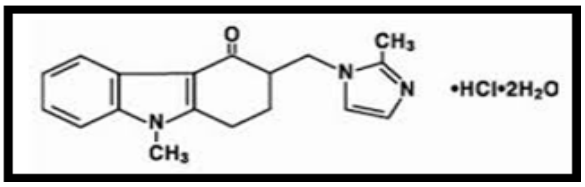

Fig. 1: Structure of the Ondansetron hydrochloride

Ondansetron hydrochloride is a selective 5-HT3 receptor antagonist. While its mechanism of action has not been fully characterized, Ondansetron is not a dopamine receptor antagonist. It is well absorbed from the gastrointestinal tract. Serotonin receptors of the 5-HT3 type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor tigger zone of the area postrema [11].

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Theory of FDDS:

Buoyancy capability of floating matrix systems [12] and sinking of non-floating forms is determined using an apparatus to quantitatively measure the total force acting vertically on the immersed object.

It was given by the vector sum of buoyancy F(b) and gravitational forces F (g) acting on the test object.

$$F = F(b) - F(g)$$
$$F = (df – ds)\ gv = (df - w/v)\ gv$$

Where,

F = resultant weight of the object, df, ds = fluid density and solid object density, g = acceleration due to gravity, w, v = weight and volume of the test objects.

Online continuous floating monitering system to provide quantitative measurement of resultant floating force was explained by the equation,

$$F = (\rho m – \rho c)\ gVc$$

ρ m, ρc = density on which the tablet floats, test object. Vc = volume of test object, Pc, Vc are important for overall floating force.

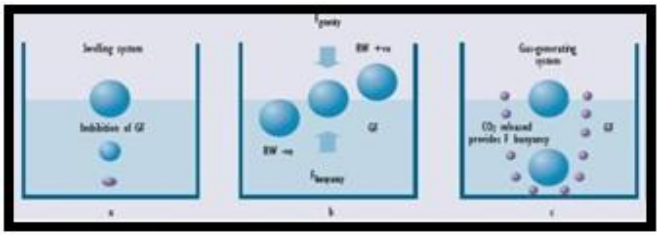

Fig. 2: Mechanism of floating systems of floating matrix tablets

MATERIALS AND METHODS

Ondansetron Hydrochloride, Kondagugu gum, Sodium alginate, Calcium carbonate Sodium Bicarbonate, Citric acid, Micro crystalline cellulose, Magnesium Stearate. Ondansetron hydrochloride is obtained as a gift sample from Dr.Reddy's Laboratories, Hyderabad.

Ondansetron hydrochloride is a selective blocking agent of the serotonin 5-HT3 receptor type, belonging to BCS class III. The IUPAC name of Ondansetron is 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one,monohydrochloride, dihydrate.

Preformulation:

API Characterization: Determination of melting point:

The melting point of Ondansetron hydrochloride drug was determined using capillary tube and was uncorrected.

Fourier transformer infrared (FTIR) spectroscopy, Powder X-Ray diffraction study of model drug (PXRD) & DSC:

FTIR spectrum of Ondansetron hydrochloride was obtained using FTIR spectrophotometer, by Kbr pellet method. Crystallinity of the drug was determined using the Bruker D8 advance XRD with copper target .The condition were 40 KV voltages; 40mAcurrent; at room temperature.

Formulation Development:

Procedure:

In direct compression, drug and all other Excipients were firstly passed through sieve, and mixed homogeneously in geometrical proportion.

Table No. 1: Different formulations from F1-F9

Code	Drug (mg)	Hupp Gum (mg)	Sodium Alginate (mg)	$CaCo_3$* (mg)	$NaHCo_3$* (mg)	Citric Acid (mg)	Mcc* (mg)	MgSt* (mg)	Total wt (mg)
F1	5	7.5	45	16.5	27	9	38.9	1.5	150
F2	5	26.5	45	16.5	27	9	19.4	1.5	150
F3	5	45	45	16.5	27	9	0.9	1.5	150
F4	5	7.5	26.5	16.5	27	9	57	1.5	150
F5	5	26.5	26.5	16.5	27	9	38	1.5	150
F6	5	45	26.5	16.5	27	9	19.5	1.5	150
F7	5	7.5	7.5	16.5	27	9	76	1.5	150
F8	5	26.5	7.5	16.5	27	9	57	1.5	150
F9	5	45	7.5	16.5	27	9	38.9	1.5	150

** Calcium carbonate* Sodium bicarbonate* Microcrystalline cellulose, * Magnesium Stearate*

Formulation evaluation:

Evaluation of Ondansetron hydrochloride floating matrix tablets:

Tablets was evaluated for parameters such as Weight variation, Thickness, Hardness, Friability, *In vitro* buoyancy studies, Swelling index, Drug content, *In-vitro* drug release using 900ml of 0.1 N HCl at 37.5 ± 0.5°C at 50 rpm and analyzed at 310 nm. Stability study was carried out for the optimized formulation for 25°C/ 60±5% RH. 40°C/75±5% RH and samples were withdrawn at the end of 0, 1,2 and 3months and evaluated for total floating time, floating lag time and % drug release.

RESULTS AND DISCUSSIONS

Analytical Method:

Estimation of λ max of Ondansetron hydrochloride:

A suitable spectrophotometric coupled analytical method was developed for the estimation of the concentration of drug .In this content the λ max of Ondansetron hydrochloride was initially determined and subsequently a calibration curve in 0.1N HCl was constructed.

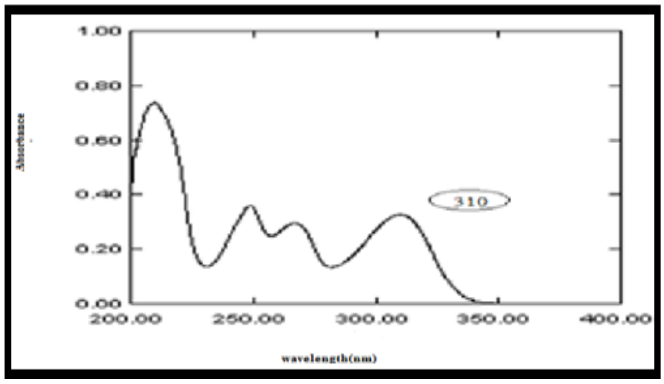

Fig. 3: UV spectrum of Ondansetron hydrochloride (con.8µg/ml in 0.1N Hydrochloric acid)

Data for Standard calibration curve:

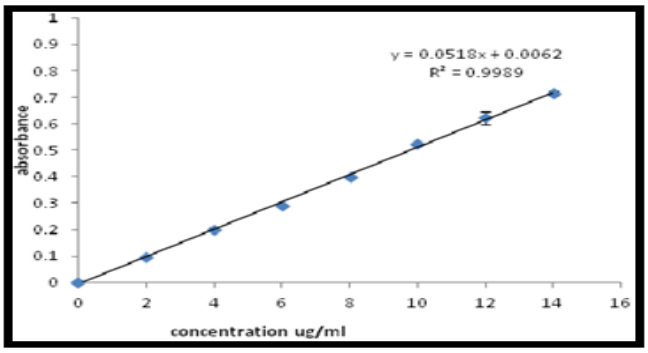

Fig. 4: Standard plot of Ondansetron hydrochloride in 0.1N Hydrochloric acid at 310 nm

The λ max ondansetron hydrochloride was observed at 310 nm.The standard graph constructed conferred that the concentration of the drug ranging from 2 to 12µg/ml obeyed the Beer-Lambert principle.

Preformulation:

API Characterization: The FTIR spectrum of the drug was recorded.

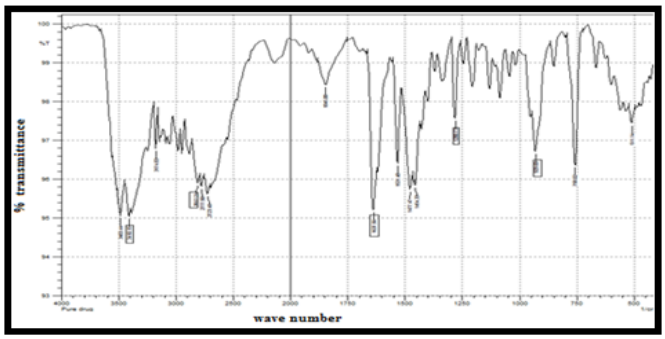

Fig. 5: FTIR spectra of Ondansetron hydrochloride

DSC thermogram of Ondansetron Hydrochloride:

The DSC analysis of the drug revealed an endothermic peak at around 184.53 ° C.

For identification of the drug melting point was determined .In the thermogram of the pure drug, endothermic corresponding to the melting point of drug was appeared at 184.5°C.

PXRD of Model drug:

Crystallinity of the drug was determined using Bruker D8 advance XRD. In this the X-ray diffraction patterns were analyzed. Peaks observed in the X-ray diffraction pattern indicate the crystalline nature of the model drug.

Drug Excipient compatability studies:

The FTIR spectra were recorded to study the interference of drug with the Excipients.

A comparison of the infrared spectral analysis of the drug in pure form and in mixture of excipients, revealed no difference in peaks of Ondansetron hydrochloride. Hence, it was providing an evidence for the absence of interaction between Excipients.

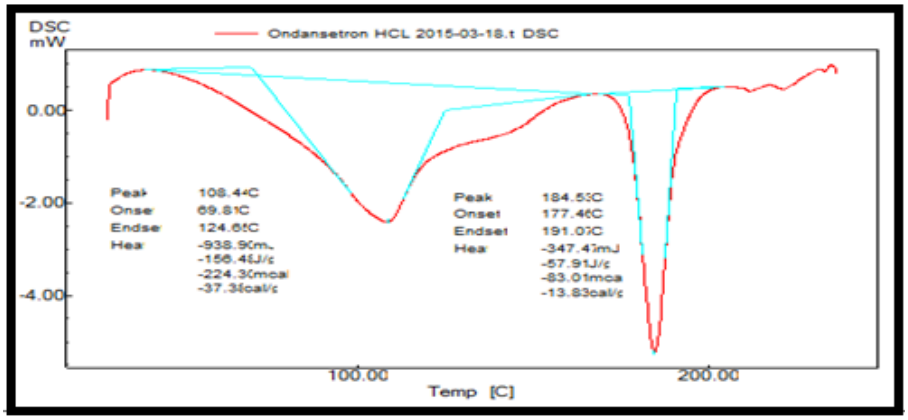

Fig. 6: DSC thermogram of Ondansetron Hydrochloride

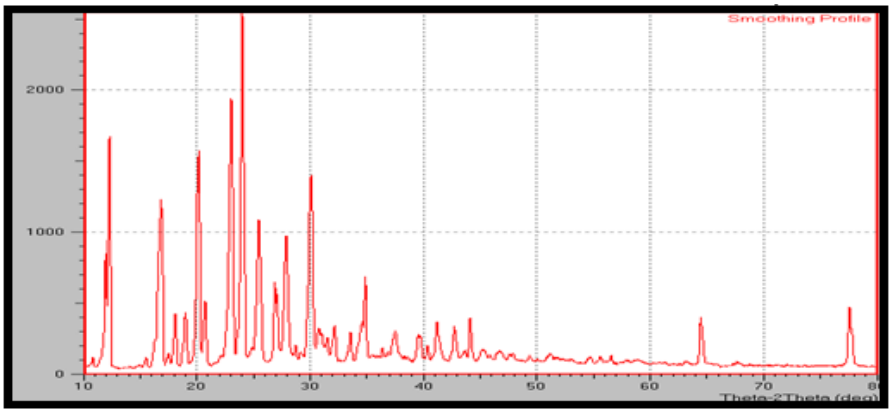

Fig. 7: PXRD pattern of model drug

Drug Excipient compatibility studies using FTIR:

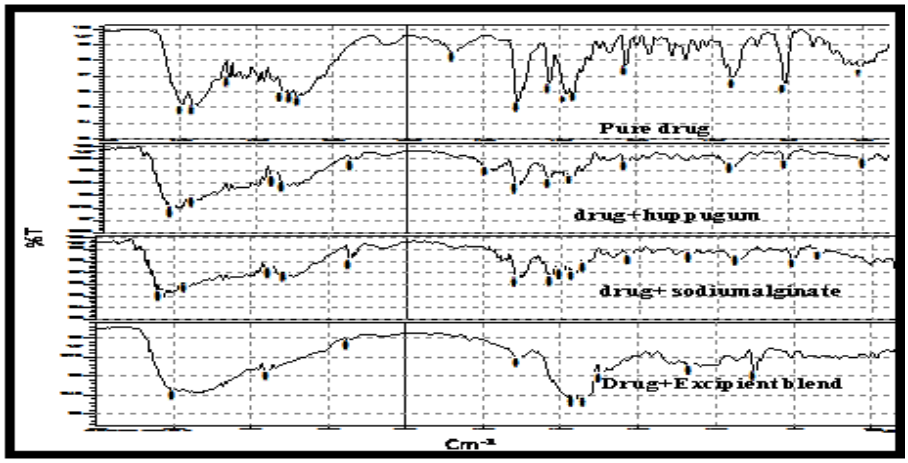

Fig. 8: Comparison of FTIR spectra of Ondansetron hydrochloride with different polymers and blend

Table No. 2: Comparison of IR Characteristic peaks of pure drug and in combination with excipient in the spectra

Name	C-H stretching (cm^{-1})	C=O stretching (cm^{-1})	C-N stretching (cm^{-1})	O-H bending (cm^{-1})	N-H Stretching (cm^{-1})
Pure drug	2812.21	1637.99	1280	3410.15	3174.33
Drug+Huppu gum	2883.58	1641.42	1278.81	3415.93	3176.83
Drug+Sodium alginate	2883.54	1641.42	1280 .73	3415.93	3204.09
Drug+Excipient blend	2887.58	1641.42	1280 .73	3496.94	3199.56

Drug Excipient Compatibility using UV Spectrophotometry:

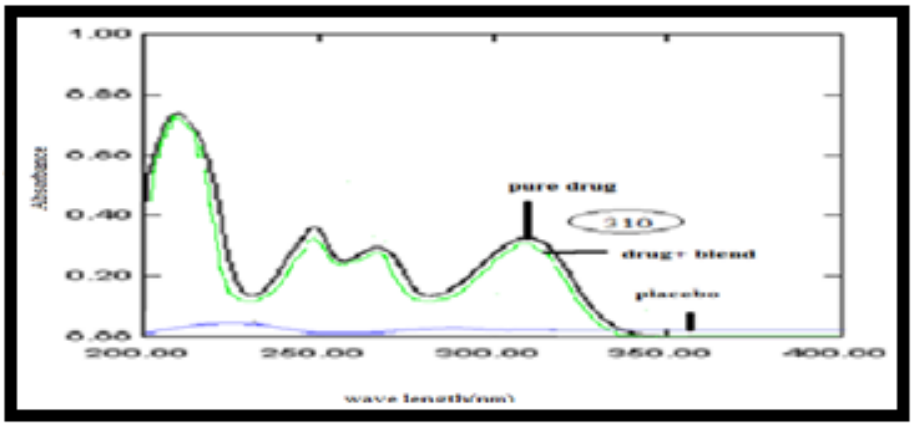

Fig. 9: Comparative UV spectrum of Ondansetron hydrochloride with excipient blend (8µg/ml in 0.1N hydrochloric acid)

Table No. 3: Evaluation of pre-compression parameters

Code	Bulk density (gm/ cm^3) (A.M±S.D)	Tapped density (gm/ cm^3) (A.M±S.D)*	Carr's index (%) (A.M±S.D)*	Hausner's ratio (A.M±S.D)*	Angle of repose(°) (A.M±SD)*
F1	0.587±0.052	0.720±0.009	16.232±0.201	1.201±0.065	31.61±0.110
F2	0.593±0.015	0.730±0.023	16.133±0.110	1.403±0.011	28.11±1.022
F3	0.606±0.005	0. 740±0.007	16.461±0.101	1.164±0.041	27.21±1.281
F4	0.591±0.011	0.753±0.007	21.221±0.021	1.262±0.032	28.10±0.211
F5	0.596±0.002	0.690±0.002	17.230±0.041	1.171±0.014	26.81±0.570
F6	0.593±0.001	0.705±0.006	16.165±0.110	1.184±0.062	28.90±0.952
F7	0.596±0.005	0.740±0.005	21.163±0.151	1.128±0.061	26.81±0.646
F8	0.586±0.001	0.665±0.020	14.022±0.037	1.108±0.060	26.10±0.362
F9	0.592±0.005	0.710±0.001	15.631±0.250	1.118±0.104	28.11±1.021

**values are mean of three determinations.*

Table No. 4: Evaluation parameters of F1-F9 formulations

F.Code	Weight variation* (mg) (A.M± S.D) n=20	Hardness* (kg/ cm^2) (A.M±S.D) n=5	Thickness* (mm) (A.M±S.D) n=5	Friability* (%) (A.M±S.D) n=6	Drug content* (A.M± S.D) n=3
F1	149.7±0.210	5.8±0.018	0.94±0.101	0.33±0.111	94.30±0.112
F2	149.9±0.052	6.2±0.013	0.97±0.015	0.35±0.201	99.81±0.072
F3	149.9±0.110	6.5±0.015	0.98±0.032	0.34±0.731	90.47±0.107
F4	149.7±0.511	5.7±0.036	0.92±0.072	0.25±0.121	94.20±0.019
F5	150.0±0.052	6.0±0.022	0..91±0.006	0.32±0.110	96.40±0.116
F6	149.9±0.111	6.5±0.044	0.92±0.021	0.32±0.320	91.34±0.118
F7	150.1±0.570	5.8±0.052	0.89±0.043	0.34±0.341	95.73±0.097
F8	149.6±0.411	5.8±0.055	0..88±0.042	0.31±0.452	96..62±0.115
F9	150.1±0.601	6.5±0.022	0.90±0.015	0.34±0.342	92.34±0.128

**values are mean of three determinations.*

The weight variation of the prepared tablets indicated no significant difference in the weight of individual tablets from the average value. In all the formulations the hardenss test indicates good mechanical strength. Friability of all formulations was less than 1% which indicates the tablets had good mechanical resistance.

Evaluation of Buoyant Properties:

Table No. 5: Floating lag time, total floating time of various formulations

Code	Floating lag time (sec) (AM ± SD)*	Total floating time (hr)
F1	38 ±2.001	>12
F2	34±1.522	>12
F3	48±1.000	>12
F4	41±1.010	>12
F5	60±2.000	>12
F6	78±0.158	>12
F7	50±2.200	>12
F8	68±1.513	>12
F9	80±1.110	>12

** Values are mean of three determinations*

The floating of the tablets was accompanied by incorporating gas generating agents (sodium bicarbonate and citric acid) into the swell able hydrophilic polymer matrix. As the dissolution medium was inhibited into the matrix, the interaction of fluid with the effervescent base took place, resulting in the formation and entrapment of carbon dioxide gas within swollen gel, thus causes floating. All the batches of the tablets exhibited desired floating time (34-80 sec) and floating duration (>12) hrs. The Swelling index studies of tablets were performed by all the formulation. They showed swelling with diffusion mechanism, which took place by retardation of water. Which were based on concentration of Kondagugu gum and sodium alginate.

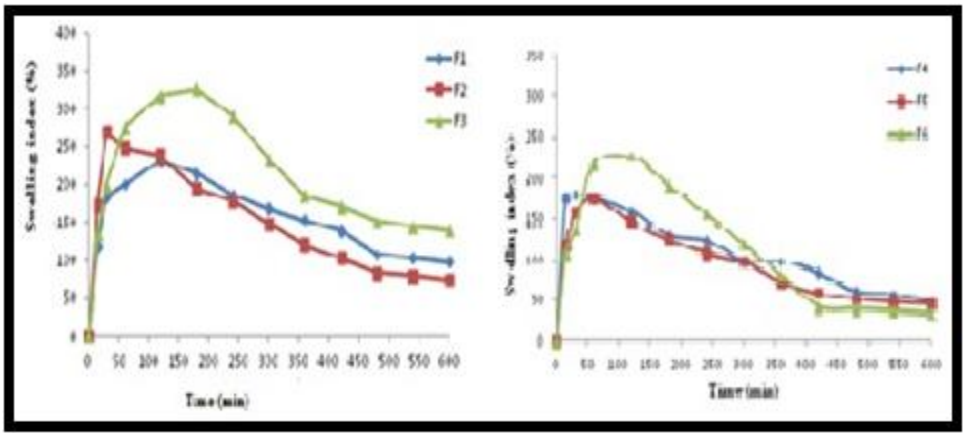

Fig. 10: Swelling index of formulations (F1-F6)

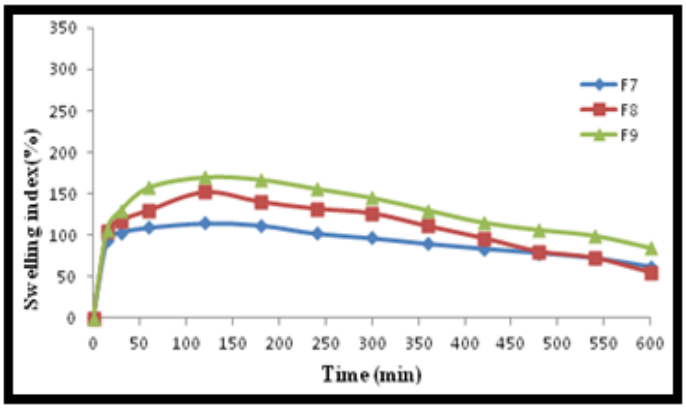

Fig. 11: Swelling index of formulations (F7-F9)

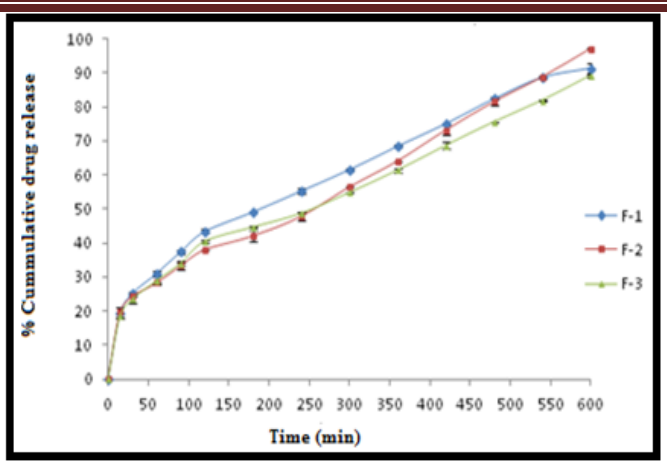

Fig. 12: *In vitro* drug release profile of formulations F-1,F-2,F-3

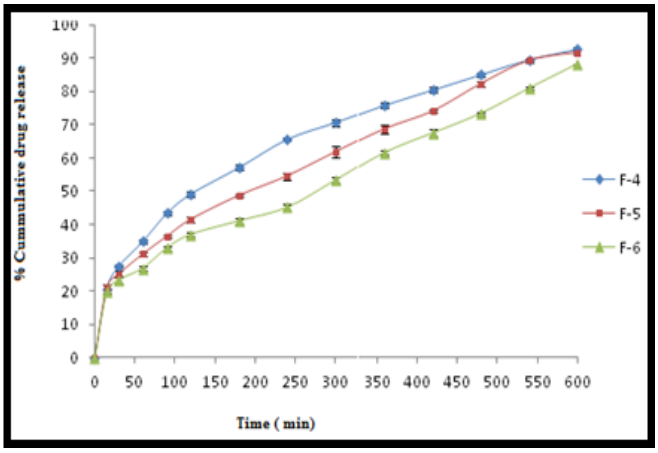

Fig. 13: *In vitro* drug release profile of formulations F-4,F-5,F-6

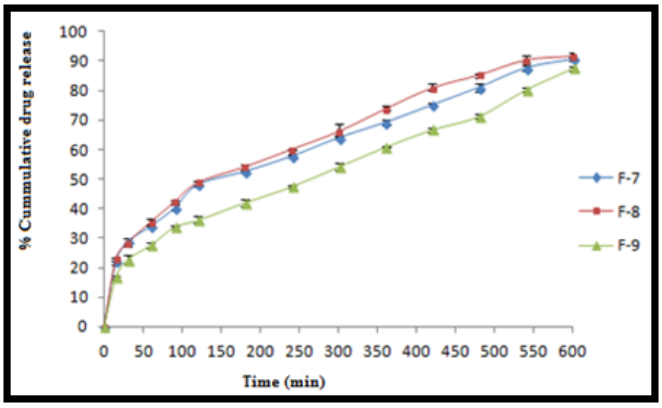

Fig. 14: *In vitro* drug release profile of formulations F-7,F-8,F-9

Sodium alginate was added as a gelling agent to enhance the dissolution rate of the drug .In contrast kondagugu gum was incorporated to sustain the drug release .The *in vitro* dissolution studies of preparation revealed that Kondagugu gum behaves differently depending on the proportions used. It forms a protective boundary layer and retards the diffusion of water molecules into core of the matrix there by extending the drug release.

Tablets showed better sustainability probably because of gradual swelling and erosion of gel layer, as the gel layer formed results in increase of diffusion path length of drug molecules. A comparison of the release profiles of the different formulations showed that tablets of Kondagugu gum, sodium alginate gave good sustained drug release pattern.

Drug-Excipient compatibility studies of optimized compatibility:
FTIR analysis:

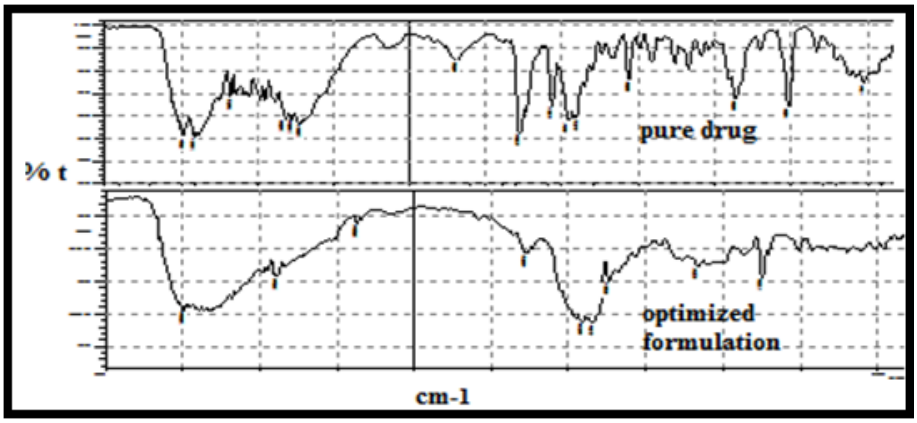

Fig. 15: Comparison of pure drug and Optimized formulation (F-2) IR spectrums

XRD:

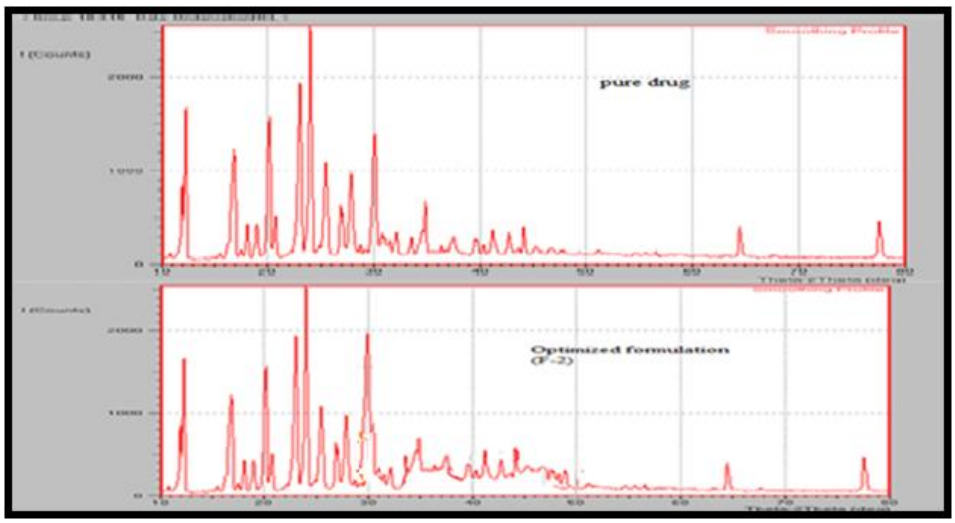

Fig. 16: PXRD of pure drug and optimized formulation (F-2)

X-ray diffraction of Ondansetron hydrochloride confirms is crystalline nature as evidenced from number of sharp intense peak.

Fig. 17: Picture of swelling index studies of optimized formula (F-2) after 10 hours

(a) (b) (c)

Fig. 18: Floating time of optimized formulation at (a) 5min; (b) 5hr; (c) 12hr

Comparison of cumulative drug release of optimized formulation with that of pure drug.

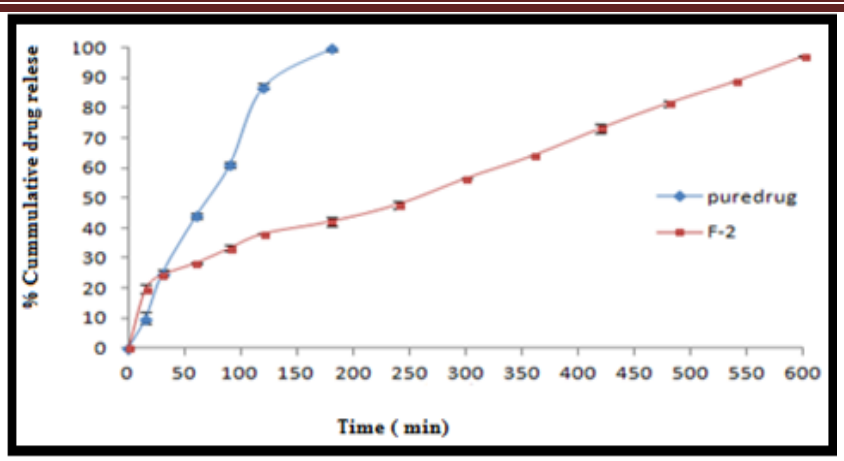

Fig.19: *In vitro* dissolution profile of optimized formulation (F-2)

Table.6: Stability study results of Optimized formulation

Parameters	Initial		1 month		2 month		3 month	
Humidity condition	25°C 60±5%RH	40°C 75±5%RH	25°C 60±5%RH	40°C 75±5%RH	20°C 60±5%RH	40°C 75±5%RH	25°C 60±5%RH	40°C 75±5%RH
Physical appearance	Cream colour	Cream colour	No change	No change	No change	No change	No change	No change
Total floating time (hr)	>12	>12	>12	>12	>12	>12	>12	>12
Floating lag time (sec) (A.M±S.D)*	34±2.01	35±1.02	32±0.97	33±1.20	29±0.98	30±0.92	34±1.23	35±2.03
%DR(10hr) (A.M±S.D)*	97.11±1.20	97.15±0.98	97.09±1.32	96.90±0.94	97.01±1.24	96.86±1.2	97.25±1.02	96.13±0.98

** Values are mean of three determinations*

CONCLUSIONS

The focus of this research work was to formulate different batches of floating matrix tablets and investigated it's *in vitro* buoyancy properties as well as release characteristics using Ondansetron hydrochloride as a model drug. Formulation was designed by considering blend ratio of Kondagugu gum and sodium alginate then direct compression technique was used and formulated 9 formulations. Among the various formulations used in the study, one of the, formulation F-2 exhibited good floating time and sustainability in drug release up to 10 hrs. The drug release from developed formulations was found to be inversely proportional to kondagugu gum concentration in the matrix. The results of *in-vitro* studies and mathematical modeling of release showed the release pattern of Zero order. Hence, it is concluded that Ondansetron hydrochloride was successfully formulated as gastro retentive floating tablets with improved gastric retention and sustained drug release.

AKNOWLEDGEMENTS

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