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FORMULATION DEVELOPMENT AND EVALUATION OF FLOATING OSMATIC DRUG DELIVERY SYSTEM FOR MODEL DRUG

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ABSTRACT
This study was conducted to develop floating osmotic tablets of Manitol, a H2 receptor antagonist, to release the drug as two distinct pulses separated by a lag time that achieve plasma concentration profiles varying in a circadian rhythm fashion, for the chronotherapy of ulcer. Floating osmotic tablets were developed using effervescence method consisted of three different steps viz, preparation of floating sustained release drug containing tablets followed by time-lagged (4 hrs) coating with hydrophobic rupturable polymer, ethyl cellulose (EC), and finally compression coating with immediate release dose of Mannitol and supporting buoyant layer. Three ratios of Ethyl cellulose to HPMC E15 (32.5:67.5, 50:50, and 67.5:32.5) at three coating levels (5%, 10%, 15%) were used to optimize the lag time (4 hrs). Carbopol 934P, cross povidone and sodium bicarbonate were used in buoyant layer. The developed floating osmotic tablets by effervescence method were evaluated for pre-formulation parameters, weight variation, thickness, hardness, friability, drug content, content uniformity, In-vitro floating properties, and In-vitro drug release. The optimized formulation provided expected two-phase release pattern of Mannitol with initial immediate dose release in 30 min and then lag time 4 hrs of no drug release followed by sustained release for 8hrs in stomach during floating.

KEYWORDS: Pulsatile drug delivery systems; Gastric retention; Chronopharmacokinetics; Mannitol.

INTRODUCTION
Introduction Chronotherapeutic drug delivery system is one of advanced approach used to increase effectiveness of the drug.[1] Human body physiological functions vary with time in a day, these variations cause fluctuations in plasma drug concentration. Circadian variation in most of the diseases such as Asthma, Hypertension, and Gastric Ulceritis lead to the development of site specific drug delivery associated with time–scheduled drug release shown in Figure 1; For example in early hours of the day patients encountered with more chances of heart stroke than in the other timings of the day ,asthma aggravates in early morning and in midnight than in the rest of the day as well as body stiffness associated with inflammation in early hours of morning.[2-4] To benefit from the drug therapy dosage form were taken by the patient before sleep, enabling the dosage forms to release drug completely.

MATERIALS
Materials Mannitol was obtained as gift sample from MSN Laborotories,Pvt.Ltd. Hyderabad and other excipients HPMC K4M, Lactose, Magnesium stearate, Talc, Sodium bicarbonate, Carbopol 934P, Cross povidone, Ethyl cellulose 50Cps, HPMC E 15, Dibutyl phthalate, Iso propyl alcohol, Conc. Hydrochloric acid, carbopol 934, Aerosil were obtained from S.D. Fine Chemicals, Mumbai.

METHODOLOGY
Floating osmotic tablets of Mannitol were prepared using Effervescence method Here floating osmotic tablets of Mannitol were formulated in 3 steps.
They are.
Step 1: Formulation of floating tablets (Direct compression)
The composition of different formulations of Mannitol floating core tablets are shown in Table 1. Three formulations were prepared and coded them from F1 to F3.
Step 2: Formulation of floating osmotic tablets (Spray coating) Coating solution formula (8%w/w polymer solution

FORMULATION DEVELOPMENT
Procedure for formulation development

- PREPARATION OF CORE TABLETS (Drug and osmogen)

- COATING OF CELLULOSE ACETATE (Osmotic layer)
- COATING OF FLOATING LAYER (HPMC and sodium bicarbonate)
- COATING OF ENTRAPMENT LAYER (Eudragit RL 30D**)**

Step 3: Formulation of floating osmotic tablets of Mannitol with immediate release dose (Compression coating) All the ingredients in the Table 3 were accurately weighed and to this sodium bicarbonate as a gas generating agent, passed through sieve no. 20 was added and blended thoroughly. 50% w/w (of the tablet) of the above powder was added to the die cavity and then the optimized floating osmotic release tablet (CF8) was placed exactly at the centre of the die on the powder. To it remaining 50% w/w (of tablet) of the above powder was added as shown in such a way that the osmotic release tablet was fully covered on its upper crown, encapsulating rest of the tablet in the powder. It was then compressed using multi station tablet punching machine using 12 mm punches (Table 3). Evaluation of Floating Osmotic Tablets of Mannitol Preformulation studies (drug-excipient interaction studies, flow properties) were carried out for powder blends to detect any interaction between drug and excipients and to determine the flow properties of ingredients. Prepared tablets were evaluated for post compression parameters like various quality control tests such as Tablet thickness and Diameter, Hardness, Friability, uniformity of weight and content uniformity of drug and drug release and other specific evaluation tests for GFDDS like floating lag time and total floating time. Drug-excipient interaction studies Fourier transforms infrared spectroscopy: The Infrared spectra of Mannitol pure drug, exipients, physical mixture of drug and excipients (Optimised formula-CCF3) were recorded between 400 to 4000 cm-1. The IR spectra were obtained using KBr disk method using an FTIR spectrophotometer.[13]

PROCEDURE FOR EVALUATION

Physical evaluation in 250ml of 0.1N HCl solution.

Operating Conditions for dissolution study

Parameter	**Details**
Dissolution apparatus	Type II (USP)
Rotations per minute (rpm)	50
Temperature	37± 0.5 ºC
Medium	1.2PH HCl solution.
Sample volume withdrawn	8 ml
Time points	1, 2, 3, 4, 6, 8, 10, 12, 14 hrs.
Analytical method	Ultraviolet Visible Spectroscopy
λ max	271 nm

Procedure for formulation development

PREPARATION OF CORE TABLETS

Core tablets composed drug and other excipients (MANNITOL AS OSMOTIC AGENT,SODIUM BICARBONATE AS EFFERVESCENT AGENT) were prepared by direct compression method.

COATING OF OSMOTIC LAYER

Coating composition

Polymer	Cellulose acetate
Plasticizer/Pore former	PEG400
Solvent	Acetone: water(90:10)
Solid content	6%w/w

HI-COATER: Coating parameters

Parameter	Operating condition
Pan rotations	14-18rpm
Inlet temperature	28-30^{0}C
Bed temperature	20-24^{0}C
Spray rate	5-7ml/min

COATING OF ENTRAPMENT LAYER

Coating composition

Polymer	**Eudragit RL 30D**
Plasticizer	TEC
Coating aid	Talc
Solvent	Water
Solid content	15%w/w

Coating Parameters

Parameter	**Operating condition**
Pan rotations	16-20rpm
Inlet temperature	85-90^{0}C
Bed temperature	38-42^{0}C
Spray rate	3-5ml/min

Formulations, observations and inferences
Formulation 1.
Both swellable polymer and effervescent agent for floatability of the core.

Formulation 1:

Both **swellable polymer and effervescent agent** for floatability of the core.

	Ingredients	mg per tablet
Core tablets:	Drug	100
	Mannitol SD 200	200
	Pregelatinized starch	100
	Methocel K4M	100
	Sodium bicarbonate	25
	Citric acid	25
	Magnesium stearate	5
	Total weight	455
Coatings	Coating Composition	Weight gain (%)
	Semi-permeable layer: CA:PEG 400(1:0.2)	**10**
	Floating layer: HPMC E15:NaHCO3:PEG6000 (6:4:0.6)	**5, 15.**
	Entrapment layer: EudragitRL30D: TALC:TEC (1:0.35:0.2)	**2, 4, 6, 8.**

Observations /results and discussion:
Without entrapment layer coating.

Coating percentage (Semi-permeable layer+ floating layer +entrapment layer)	Floating lag time	Floating time
10+5+0	20 sec	20 min
10+15+0	50 sec	60 min

•**solubilization and erosion** of floating layer

With different coating percentage of entrapment layer:

Coating percentages (Semi-permeable layer + floating layer + entrapment layer)	Floating lag time (min)	Floating time (hrs)
10+5+2	7-8	4.5
10+5+4	9-10	5.5
10+5+6	12-13	7.5
10+5+8	15	>8

Burst of entrapment and osmotic layers were observed at later part of the dissolution time points which is due to **swelling of polymer** present in the core tablets.

Formulation 2, 3, 4, 5, 6, 7:To prevent the bursting of osmotic layer.

- **Different swellable polymers.**
- **Concentration of swellable polymer was 25mg**

Ingredients(mg/tab)	F2	F3	F4	F5	F6	F7
Model drug	100mg	100mg	100mg	100mg	100mg	100mg
Mannitol SD200	200mg	200mg	200mg	200mg	200mg	200mg
Methocel K4M,	25mg	--	--	--	--	--
Xanthan gum,	--	25mg	--	--	--	--
Klucel HF,	--	--	25mg	--	--	--
PVP K-90	--	--	--	25mg	--	--
Polyox N80	--	--	--	--	25mg	--
Sodium bicarbonate	25mg	25mg	25mg	25mg	25mg	25mg
Citric acid	25mg	25mg	25mg	25mg	25mg	25mg
Magnesium stearate	5mg	5mg	5mg	5mg	5mg	5mg
Total weight	380 mg	380 mg	380 mg	380 mg	380 mg	355 mg

Pore former 10% Weight gain 10%

Observations /results and discussion

Burst of osmotic system was observed within one hour at dissolution conditions, irrespective of polymer type, even the formulation without polymer (F7) showed bursting. Bursting of osmotic system may be due to rapid release of carbon dioxide gas.

Formulation 8,9,10: To optimize the floating and entrapment layer composition.

without swellable polymer and effervescent agents in the core tablet.

Core tablets.

Ingredients	mg per tablet
Drug	100
Mannitol SD 200	100
MCC(102)	100
Sodium bicarbonate	0
Citric acid	0
Magnesium stearate	5
Total weight	305
Coating-Composition	Weight gain (%)
Semi-permeable layer : CA:PEG 400(1:0.2)	10
Floating layer: HPMC :NaHCO3:PEG6000 (6:4:0.6)	5
Entrapment layer: Eudragit RL 30D:TALC:TEC	4, 6, 8.

Formulation 8: Talc concentration in entrapment layer was 35 % .

Formulation 9: Talc concentration in entrapment layer was reduced from 35 % to 15%.

Formulation 10: Methocel E50 was used instead of Methocel E15.

Observations /results and discussion:

Coating percentages: (Semi-permeable layer + floating layer + entrapment layer)	Formulation 8 Floating-lag time (min)	Formulation 8 Floating time (hrs)	Formulation 9: Floating lag time (min)	Formulation 9: Floating time (hrs)	Formulation 10 Floating lag time (min)	Formulation 10 Floating time (hrs)
10+5+4	8	3	7.5	1	4	**8-16**
10+5+6	9	5	8	1.5	6	
10+5+8	11	8	11	3.5	7	

This floating composition (F10) of floating layer and entrapment layer was used for further studies. Floating time can be improved by incorporation of sodium bicarbonate in the core tablet.

Formulation 11

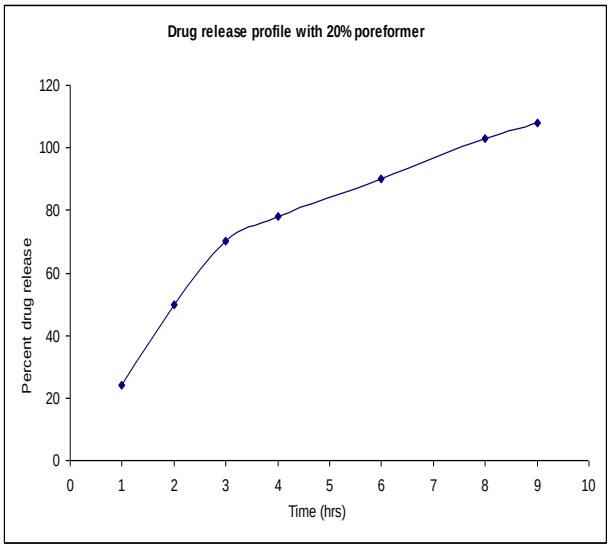
Core tablets containing effervescent agents and coating of Semi-permeable layer with increased amount of pore former(F7 with 10% pore former was bursting)

Core tablets:

Ingredients	mg per tablet
Drug	100
Mannitol SD 200	200
Sodium bicarbonate	25
Citric acid	25
Magnesium stearate	5
Total weight	355

Pore former content in osmotic layer coating for formulation 11.

Formulation	Pore former content
F11	**20%**



The drug release was more than 50% at 2 hr dissolution time point due to high pore former level in osmotic layer and high solubility of drug. So,20% pore former is not a suitable level to control the drug release. Burst of osmotic system is not observed due to high pore former content, aiding release of gas from the system.

Formulation 12

As formulation 7 was bursting and formulation 11 was showing faster drug release, Osmotic core tablets were prepared without effervescent agent and coated with osmotic layer having 10% pore former for 10% weight buildup.

Core tablets

Ingredients	mg per tablet
Drug	100
Mannitol SD 200	250
Sodium bicarbonate	0
Magnesium stearate	5
Total weight	355

Formulation 13 and 14

To evaluate effect of cellulose acetate coating percentage on drug release from delivery system.

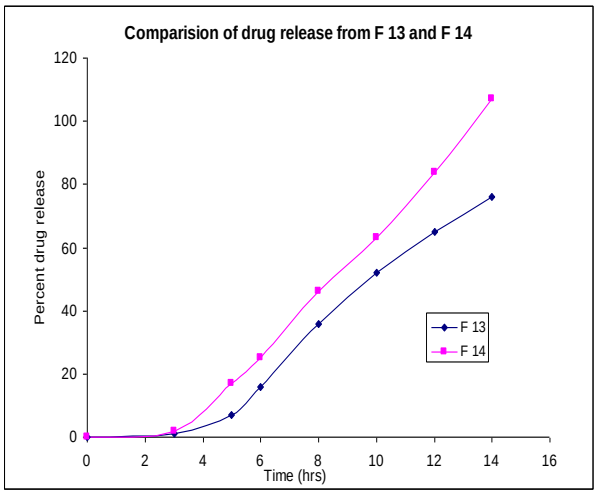
4% and 10% cellulose acetate coating.

Core tablets for formulation 13 and 14,

Ingredients	mg per tablet
Drug	100
Mannitol SD 200	250
Sodium bicarbonate	0
Magnesium stearate	5
Total weight	355

Coating for formulation 13 and 14.

Coating	Weight gain (%)(F13)	Weight gain (%)(F14)
Semi-permeable layer :	**10**	**4**
Floating layer:	5	5
Entrapment layer:	8	8



System with 4% CA coating (F 14) shows **faster** drug release compared to system with 10% CA coating (F 13). But odd tablets were sinking in between **8-16hrs.** So incorporation of small amounts of sodium bicarbonate in the core tablet may improve the floating time. Both the systems show very less drug release at initial time points which has to be improved.

Formulation 15

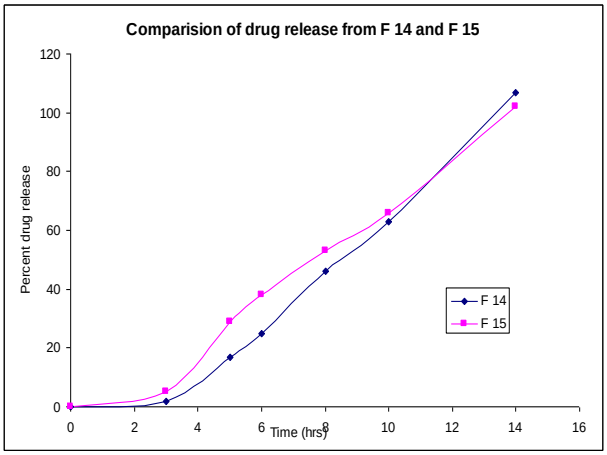
To evaluate the effect of sodium bicarbonate on floating time and drug release core tablets with sodium bicarbonate(12.5mg) were prepared and compared with F14 (without sodium bicarbonate).

Core tablets

Ingredients	mg per tablet
Drug	100
Mannitol SD 200	237.5
Sodium bicarbonate	**12.5**
Magnesium stearate	5
Total weight	355

Coating

Coating	Weight gain (%)
Semi-permeable layer	4
Floating layer	5
Entrapment layer	8



Drug release is slightly faster from the formulation with sodium bicarbonate. Drug release at earlier time points is less than 10% and this had to be improved in subsequent formulations.

Floating lag time and floating time.

Formulation	Floating lag	Floating time
F14	7-8min	16hrs, with some tablets sinking after 8hrs
F15	7-8min	24hrs

Optimization of drug release

Formulation 16 and 17

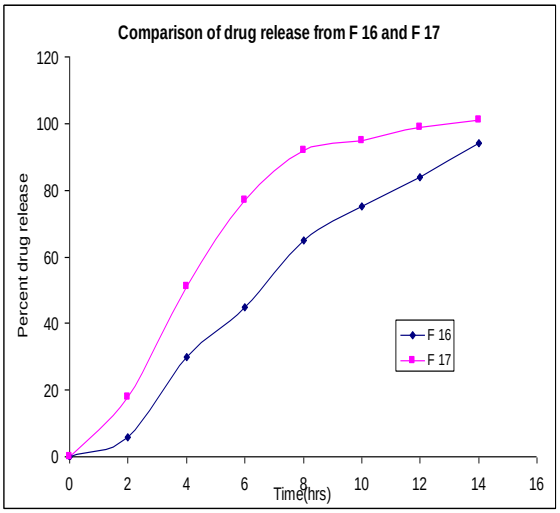
For optimization of drug release, formulations with varying **concentrations of mannitol** were formulated. Two formulations, one with 237.5mg (F16) and other with 150mg (F17) of mannitol were prepared.

Core tablets.

Ingredients	mg per tablet(F16)	mg per tablet(F17)
Drug	100	100
Mannitol SD 200	**237.5**	**150**
Sodium bicarbonate	12.5	12.5
Magnesium stearate	5	5
Total weight	355	265

Coating

Coating	Weight gain (%)
Semi-permeable layer :	4
Floating layer:	5
Entrapment layer:	4



Formulation with 150mg of mannitol shows faster release with 90% drug release in 8hrs where as formulation with 237.5mg mannitol showed slower release. Because of its high solubility, drug serves as osmogen and pushes the mannitol out of the system leading to slow and incomplete release of drug when high concentrations of mannitol is used in the core tablet.

Formulation 18 and 19

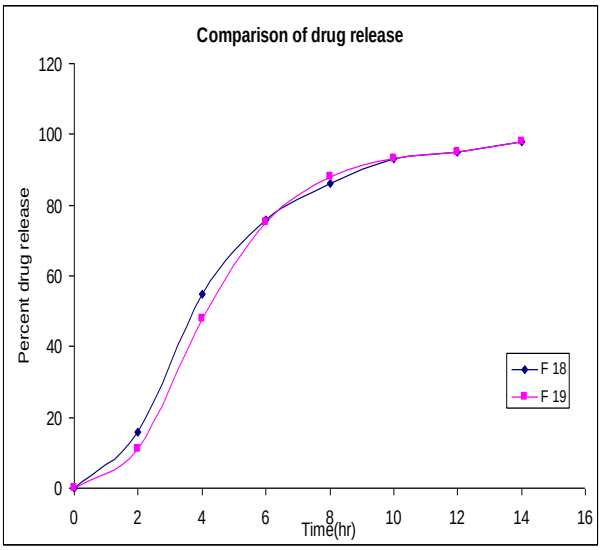
To evaluate the effect of percentage coating of floating layer on floating lag time, floating time and release profile, formulation 18 was developed with 2.5% buildup and formulation 19 was developed with 5% buildup of floating layer.

Core tablets

Ingredients	mg per tablet
Drug	100
Mannitol SD 200	150
Sodium bicarbonate	12.5
Magnesium stearate	5
Total weight	265

coating for tablets 18,19

Coating	Weight gain (%)(F18)	Weight gain (%)(F19)
Semi-permeable layer:	4	4
Floating layer:	**2.5**	**5**
Entrapment layer:	8	8



Floating lag time was 7-8min; floating time was 24hrs for both the formulations. No significant change on floating time and floating lag time was observed with increase in floating layer percentage from 2.5% to 5%. Drug release is slightly slower with 5% coating of floating layer than 2.5% coating at initial time points but there was no significance difference at later time points.

Formulation 20

As from the formulation F18 it was evident that higher concentration of mannitol retards the drug release. Formulation with increased amount of mannitol was formulated, to control/optimize the drug release.

Core tablets

Ingredients	mg per tablet
Drug	100
Mannitol SD 200	180
Sodium bicarbonate	12.5
Magnesium stearate	5
Total weight	295

Coating

Coating	Weight gain (%)
Semi-permeable layer:	4
Floating layer:	2.5
Entrapment layer:	4

Evaluation of Drug release kinetics

The drug release kinetics was evaluated for the optimized formulation (F20) by zero order and first order kinetic models and the r^2 values are compared.

Formulation	r^2	
	Zero order	First order
F20	0.957	0.9962

Based on the higher r^2 value, it can be concluded that the drug release form the optimized formulation followed the first order release kinetics.

CONCLUSION

Floating osmotic system was developed which shows floating lag time of less than 5min and total floating time up to 24hrs with extended drug release for 14 hrs. Gas entrapment layer is essential for achieving higher floating time. But, no significant effect on drug release profile. Talc concentration effected the floating time.No significant difference in floating time and floating lag time was observed at 2.5% and 5% floating layer build up. Presence of sodium bicarbonate in the core tablets improves the floating time and increases the drug release.Change of mannitol level in the core tablet alters the drug release rate.

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