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Design and development of ondansetron hydrochloride pH independent control released matrix tablets

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Abstract: The oral control drug delivery is the most acceptable delivery system for patient acceptance, industrial application and economical but still it has several challenges to design a dosage form. The gastro intestinal pHis one of the major limitations for constant drug release due to different pH variations different regions (stomach *vs* small intestine) throughout the GIT. The aim of the present research work was to develop a pH independent oral control release drug delivery of pH dependent Ondansetron HCl for the treatment of CINV or PONV. The major limitation of the drug was found burst release in SGF pH 1.2 and highly precipitation in intestinal pH (pH 6.8 phosphate buffer). The formulator is challenging to develop constant controlled drug release in entire gastro intestinal tract. The techniques involve the use of pH modulating agents and acidifying agents to achieve pH independent controlled drug release. It was found that incorporation of anionic polymer (Eudragit L100-55) with control release nonionic HPMC matrix shows pH independent drug release in both SGF pH 1.2 and pH 6.8 phosphate buffer. In conclusion it was understood that the release profile of HPMC sellable matrices of Ondansetron HCl with manipulating the micro environmental pH, at variable pH conditions provided a efficient and predictable results.

Keywords: Ondansetron hydrochloric acid; pH independent; pH modulating agent; acidifying agent; HPMC swellable matrices.

INTRODUCTION

During the last decades many oral controlled release drug delivery systems were developed by using different techniques like matrix, diffusion, dissolution and diffusion, gastro-retentive drug delivery systems etc (Manthena *et al,* 2005). The main object of control drug delivery system is to achieve constant drug release from dosage form and to maintain constant plasma concentration for the treatment of chronic diseases. But the constant drug release from dosage form is not that much easy because of the control release system is influencing by the physicochemical properties of the drug, pH, GI transmit time and food. Out of all these pH and transmit time are majorly influencing the drug release. Many drugs are weakly basic and weakly acidic in nature out of some of the drugs are shows pH dependent solubility. Weakly basic drug is highly soluble in acidic environment of the stomach in low pH (pH.1.2) when the pH was increased in intestinal pH the solubility decreased or sometimes precipitated. This type of drugs to design constant release in GIT is a challenging to the formulators.

Ondansetron hydrochloride is a serotonin sub type-3(5-hydroxytryptamine-3) receptor antagonist (Venkatesh *et al,* 2006). It is a widely used drug for the treatment of several therapeutic purposes like antiemetic especially it is used in the prevention of post operative nausea and vomiting and chemotherapy or radiation induced nausea and vomiting. It is a weakly basic drug belongs to BCS class-II. The solubility exhibits high in stomach at 37^0C (23.3 g/L) at low pH (pH 1.2) and at higher pH (6.8 pH phosphate buffer) it exhibits poor solubility (0.036 g/L). For this reason, the design of control drug delivery system is very difficult because the solubility is completely pH-dependent. So this indicates incomplete results, irregular drug absorption and fluctuations in plasma concentrations. The recommended oral dose regimen of Ondansetron hydrochloride is 8 mg, three times a day .the elimination half life ($t_{1/2}$) is relatively short, around 3-5 h . Therefore, there is a need to develop controlled release drug delivery systems to extend pharmacological action.

The availability of existing literature indicates that some of the techniques were developed previously for pH-independent drug release (Smith *et al.*, 2009). Out of that, one is gastro retentive drug delivery system in which the drug will float constantly for long period of time which is a question mark and also in-vitro/in-vivo correlation is very poor (Daisychella *et al*, 2012). And another technique was developed pH modulating agents; this technique was somewhat better but the formulator was observed some manufacturing defects, to prolonged drug release is very difficult (Pygall *et al,* 2009). The present investigation is aimed to develop a pH-independent

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control drug release dosage form of Ondansetron HCl by using the combination of HPMC K100 with Eudragit L100-55 for achieving the constant drug release irrespective of any pH and it will give assurance and useful information for novel approach to develop controlled release products commercially (Rajan *et al.*, 2013).

MATERIALS AND METHODS

Ondansetron HCl was obtained as a gift sample Pranami Drugs Pvt. Ltd., Gujrat. Hydroxy Propyl Methyl Cellulose (HPMC) was supplied by Dow Chemicals, Colorcon Asia Pvt. Ltd., Mumbai, India. EUDRAGIT L100-55 was received as gift sample from Hetero Drugs Ltd., Hyderabad. Citric acid was procured from Qualigens Fine Chemicals (a division of GlaxoSmithKline Pharmaceuticals Ltd., Mumbai, India), Lactose and Magnesium Stearate were obtained from Unichem lab (Buddi, India), respectively.

The solubility of Ondansetron HCl was determined by using simulated gastric fluid without enzymes at pH 1.2, pH 6.8 (phosphate buffer) and pH 7.4 (phosphate buffer) respectively. The solubility of the API was determined by the equilibrium solubility method. Which employs upto the saturation of a solution to obtain by stirring an excessive of API need to add in the medium until equilibrium is achieved. After equilibrating the solution was kept in shaker water bath (37 ± 1^0C) up to 24 h for maximum solubility of the drug. After that the samples were removed from shaker bath and filtered with 0.22µm nylon non-pyrogenic disposable syringe filter. The filtered solution was diluted and estimated by using UV-Visible Spectrophotometer (ELICO SL-210).

Preparation of tablets

The tablets were prepared by using API of 25mg of Ondansetron HCl, controlled release Polymers (HPMC and Eudragit L100-55), pH modulating agents citric acid (CA), Tartaric acid (TA) (varying proportions)and pH independent diluentlactose was used as a filler for adjustment of tablet weight. The powder mixture were mixed and blended in a mortar and the granulating solution (a mixture of Isopropyl alcohol and water in the ratio of 1:1) was used drop wise upto form a dump cohesive mass. The wet mass was passed through sieve no#10 and dried at 50^0C for 45min. And the dried granules were passed through #22 mesh. Talc and Magnesium stearate were accurately weighed and mixed with dry granules for lubrication and finally the blend was compressed by using 8 mm diameter flat faced die and punches (Cadmach tablet press, India). Hardness for all the formulations was adjusted to 5-6 kg/cm^2 (Monsanto hardness tester-Macro Scientific Works, Delhi, India. The tablet composition shown in the (table 1, 2, 3, 4).

Characterization of tablets

FT-IR Spectral Studies

The IR spectra for the drugs and excipients were recorded on FT-IR spectrophotometer using KB rpellet technique (1:100) at the resolution rate of 4cm^{-1}. Spectrum was integrated in transmittance mode at the wave number range 400-4000 cm^{-1}

Determination of bulk density and tapped density

Weighed quantity of powdered blend was transferred into the graduated cylinder and the volume (V_0) was measured. Then, the graduated cylinder was packed with the help of lid and cylinder was set into the density determination apparatus. The density was set for 100 tablets and then the volume (V_f) was determined. The operation was continued till the two successive readings are the same. The calculation of bulk density and tapped density were made by using following formula.

Bulk density (gm/cm3) = W/V_0……...1

Tapped density (gm/cm^3) = W/V_f……2

Where, W is weight of the powder

Hardness, Friability and thickness

The hardness of the tablet was determined with the help of Monsanto hardness tester. The tablet hardness of therandomly selected tablet was measured. The tablet friability was measured with the help of Roche friabilator. The randomly selected 5 tablets were weighed and then placed into the friabilator. After 100 revolutions the tablets were removed and dedusted. Again, individual tablet was weighed by using electronic balance and the difference in weight was calculated as percent loss. The diameter and thickness of the tablets were measured with the help of Verniercaliper, the test was carried out as per the official technique.

Drug content

The drug content uniformity was measured by using powdered tablets. From this, 100mg of powdered tablet was weighed accurately and transferred to 100ml of volumetric flask. Initially 50ml of methanol was added into the volumetric flask and sonicated for the complete solubility of drug. The volume was made upto 100ml with methanol, centrifuged the mixture and 1ml the supernatant liquid was diluted, filtered and analyzed for drug content uniformity by UV spectroscopy method at 249 nm.

Dissolution studies

The *in-vitro* drug release study was done by using USP Type-II, rotating paddle apparatus (VEEGO Instruments Corporation, Mumbai, India). The operating speed was at 50 rpm. SGF (pH1.2, 900ml) was used as dissolution medium for first 2 hand pH 6.8 phosphate buffer was used for the remaining test period. The temperature was maintained at 37 ± 0.5^0C. Simultaneously we studied both pH 1.2 and 6.8 continuously for complete drug release study. Samples were collected at pre determined time

intervals, filtered and analyzed by using UV-Visible Spectrophotometer (ELICO SL-210) at 249nm (Kalaichelvi *et al.,* 2012).

RESULTS

FT-IR studies

The FT-IR of drug (Ondansetron HCl) and excipient compatability studies was carried out by using KBr pellet technique. The ondansetron HCl exhibitedcharecteristic peaks at 3,394 and 1,633 cm^{-1}, attributed to O-H stretching and C=O stretching vibrations respectively. The physical sprectrum not showed significant shift in peaks of Ondansetron HCl and slightly changed some intensity peaks were found. And as well as optimized formulation of Eudragit L100-55 with HPMC K100 formulation were studied the band at 3,499 cm^{-1} for O-H stretching and 1,699cm^{-1} for C=O stretching were found. The results of IR srectroscopy reveal that there was no chemical interaction between Ondansetron with HPMC K100 combination of Eudragit L100-55 polymer.

Table 1: Formulation development of Ondansetron without pH modulating agents

Ingredients	Formulation			
	F1	F2	F3	F4
Ondansetron HCl	25	25	25	25
HPMC K100	25	50	75	100
PVP	5	5	5	5
Lactose	190	165	140	115
Talc	2.5	2.5	2.5	2.5
Mg stearate	2.5	2.5	2.5	2.5
Total weight	250	250	250	250

pH-dependent release of weakly basic drug*:*

From the solubility study, it was found that 100% drug was released for pure Ondansetron HCl in SGF pH 1.2 within 10 min but in 6.8 pH phosphate buffer, the drug was precipitated immediately (Reza Fathi *et al* (2014)). A large variation in drug release was observed in pH 1.2 and 6.8 pH phosphate buffer. The matrix forming the tablets were studied in different pH mediums the result was found low concentration of polymer (F1) burst release was observed in SGF pH 1.2 and precipitation was observed in pH 6.8 phosphate buffer. In high concentrations (F4) 34% drug release after 1 hourinp H 1.2 where as in pH 6.8 phosphate buffer only 7.6% drug released. By using only with HPMC matrices, we found large variation in drug release because the weakly basic drug Ondansetron HCl is highly ionized in acidic environment and in basic conditions, it was observed that drug was not compleatly released from HPMC matrix tablet Drug release is shown in fig. 2.

Influence of addition of pH modulating agents on the drug release

The pH modifiers is a common strategy to enhance the drug release rate of pH-dependent weakly basic drugs. These pH modulating agents having ability to alter the micro environmental pH in the surface of the tablet and surrounding dissolution media. These agents are having ability to maintain constant pH for during the entire period of the drug release (Mulani *et al,* 2011)). The addition of organic acids in a HPMC matrix device was found that increased drug release in 6.8 pH phosphate buffer. The choice of organic acid was based on their pKa value and solubility. In this technique, citric acid and tartaric acid were selected to maintain acidic environment in the matrix of tablet. The formulations were prepared in different concentrations of citric acid and optimize the formulation. HPMC polymer concentration formulations are listed in table no.2.The formulation $CF_1$and CF_2 containing 5% and 7.5% citric acid, the drug release were found 98.2% in 0.1N HCl and 68%in 6.8pH buffer upto 10h. So, we found that citric acid concentration was not sufficient for complete drug release. Whereas, formulations CF_3 and CF_4 Containing 10% and 15% citric acid showed better dissolution profile in both media. The drug release was found as the concentration of citric acid was increased and there is no evidence further increasing of solubility. The optimized formulation of drug release with citric acid was shown in fig. 4. And another pH modulating agent Tartaric Acid (5%, 7.5%, and 10%) was incorporated with optimized concentration of HPMC polymer and the formulations are listed in table no.3. The TF_6 formulation was observed good correlation in both dissolution media and maximum amount of drug release by the end of 14 h. The drug release was shown in fig. 3. In conclusion the addition of pH modulating agent to HPMC matrix tablets was found satisfactory results to achieve pH independent drug release but the present research study was to develop non-gastric resident Ondansetron HCl once daily pH independent control release tablets. However, the drug release was up to 24 hrs in which it was failed to achieve constant pH independent drug release.

The combination of HPMC and enteric polymer Eudragit L100-55 is one of the attractive strategies to developing pH independent drug release of weakly basic drugs the formulations was listed (table no.4). The addition of Eudragit L100-] influence drug release in basic media by lowering micro environmental pH and as well as retard drug release in acidic media by forming insoluble mass that acts as barrier of drug diffusion. The addition of acidifying agents to the HPMC matrix is act as a diffusion barrier for drug release at low pH values as it is insoluble in 0.1 N HCl. However, in phosphate buffer pH 6.8 acidifying agent dissolves and thus acts as a pore former and creates internal acidic pH in a tablet (Nikam *et al* (2011). As the pH increases the matrix begins to soluble slowly and forms a soluble salt and creates low acidic pH inside the gel layer and the drug release was shown (fig. 4).

Table 2: Composition of Ondansetron with pH modulating agent (Citric Acid)

INGREDIENTS	FORMULATION							
	CF1	CF2	CF3	CF4	CF5	CF6	CF7	CF8
Ondansetron HCl	25	25	25	25	25	25	25	25
HPMC K100	75	75	75	75	100	100	125	125
Citric acid	5%	7.5%	10%	15%	7.5%	10%	7.5%	10%
PVP	6	6	6	6	6	6	6	6
Lactose	167	159.5	152	137	134.5	127	110	102
Talc	6	6	6	6	6	6	6	6
Mg Stearate	6	6	6	6	6	6	6	6
Total weight	300	300	300	300	300	300	300	300
	Characterization							
Bulk density (g/ml)	0.479±0.03	0.480±0.03	0.481±0.03	0.479±0.03	0.466±0.03	0.470±0.03	0.490±0.03	0.488±0.03
Angle of repose (g/ml)	$27^0$23±0.02	$28^0$61±0.03	$27^0$86±0.01	$27^0$61±0.04	$28^0$60±0.04	$29^0$12±0.03	$27^0$32±0.02	$29^0$00±0.02
Hardness (kg/cm2)	6.1±0.1	6.1±0.5	6.1±0.3	6.1±0.4	6.0±0.5	509±0.2	6.0±0.3	6.1±0.5
Friability (%)	0.71±0.02	0.70±0.02	0.69±0.02	0.68±0.02	0.65±0.02	0.70±0.02	0.56±0.02	0.70±0.02
Thickness (mm)	4.5±0.09	4.5±0.09	4.5±0.09	4.5±0.09	4.5±0.09	4.5±0.09	4.5±0.09	4.5±0.09
Drug content (%)	98.2±1	98.5±2	96.9±1	98.5±3	98.5±2	96.1±2	98.5±2	98.2±1

Table 3: Composition of Ondansetron with pH modulating agent (Tartaric acid)

INGREDIENTS	FORMULATION						
	TF1	TF2	TF3	TF4	TF5	TF6	TF7
Ondansetron	25	25	25	25	25	25	25
HPMC K100	75	75	75	100	100	125	125
Tartaric acid	5%	7.5%	10%	7.5%	7.5%	7.5%	10%
PVP	6	6	6	6	6	6	6
Lactose	167	159.5	152	109.5	99.5	110	112
Talc	6	6	6	6	6	6	6
Mg Stearate	6	6	6	6	6	6	6
Total weight	300	300	300	300	300	300	300
	Characterization						
Bulk density (g/ml)	0.486±0.03	0.476±0.03	0.485±0.03	0.472±0.03	0.468±0.03	0.473±0.03	0.493±0.03
Angle of repose (g/ml)	$28^0$56±0.02	$27^0$56±0.03	$28^0$56±0.01	$28^0$56±0.04	$29^0$56±0.04	$28^0$56±0.03	$27^0$56±0.02
Hardness (kg/cm2)	6.0±0.5	6.1±0.2	6.0±0.5	6.0±0.4	5.9±0.2	6.1±0.5	6.1±0.3
Friability (%)	0.64±0.02	0.68±0.02	0.71±0.02	0.60±0.02	0.62±0.02	0.71±0.02	0.56±0.02
Thickness (mm)	4.5±0.09	4.5±0.09	4.5±0.09	4.5±0.09	4.5±0.09	4.5±0.09	4.5±0.09
Drug content(%)	98.5±1	98.7±2	97.6 ±1	95.8±3	98.0±2	96.8±2	99.3±2

Table 4: Ondansetron HCl tablets with Eudragit L100-55 by Wet granulation:

INGREDIENTS	FORMULATION						
	EF1	EF2	EF3	EF4	EF5	EF6	EF7
Ondansetron	25	25	25	25	25	25	25
Eudragit L100-55	12.5	25	50	75	75	75	100
HPMC K100	12.5	25	50	50	75	100	100
PVP	3	3	3	3	3	3	3
Lactose	241	228.5	166	141	116	91	66
Talc	3	3	3	3	3	3	3
Mg stearate	3	3	3	3	3	3	3
Total weight	300	300	300	300	300	300	300
Characterization							
Bulk density (g/ml)	0.496±0.03	0.496±0.03	0.496±0.03	0.496±0.03	0.496±0.03	0.496±0.03	0.496±0.03
Angle of repose (g/ml)	$27^0$56±0.02	$28^0$56±0.03	$26^0$56±0.01	$27^0$56±0.04	$28^0$56±0.04	$25^0$56±0.03	$28^0$56±0.02
Hardness (kg/cm2)	6.1±0.5	6.0±0.2	6.1±0.5	5.9±0.4	6.1±0.2	6.2±0.5	6.0±0.3
Friability (%)	0.54±0.02	0.72±0.02	0.64±0.02	0.59±0.02	0.64±0.02	0.74±0.02	0.54±0.02
Thickness (mm)	4.5±0.09	4.5±0.09	4.5±0.09	4.5±0.09	4.5±0.09	4.5±0.09	4.5±0.09
Drug content(%)	98.2±1	98.2±2	97.2±1	95.2±3	98.2±2	96.2±2	99.2±2

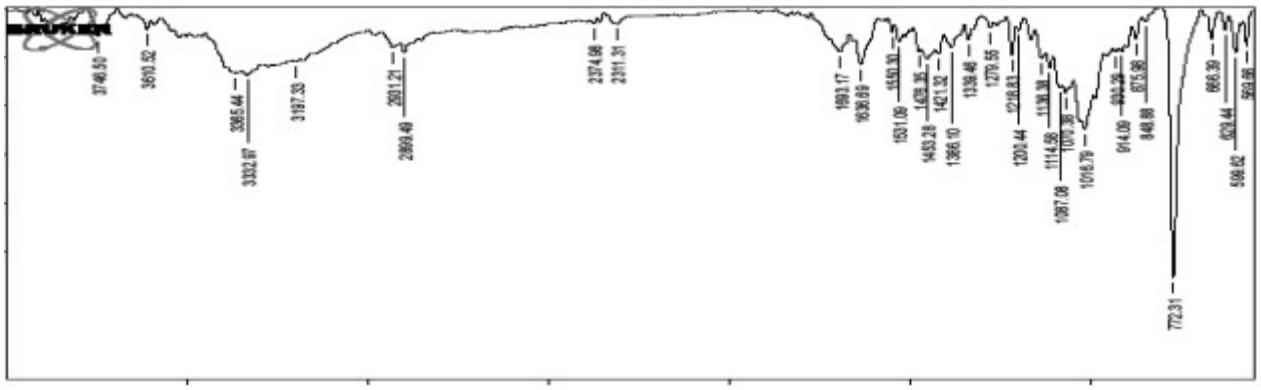

Fig. 1: IR Spectra of Optimized formula of Ondansetron HCl with Eudragit L100-55

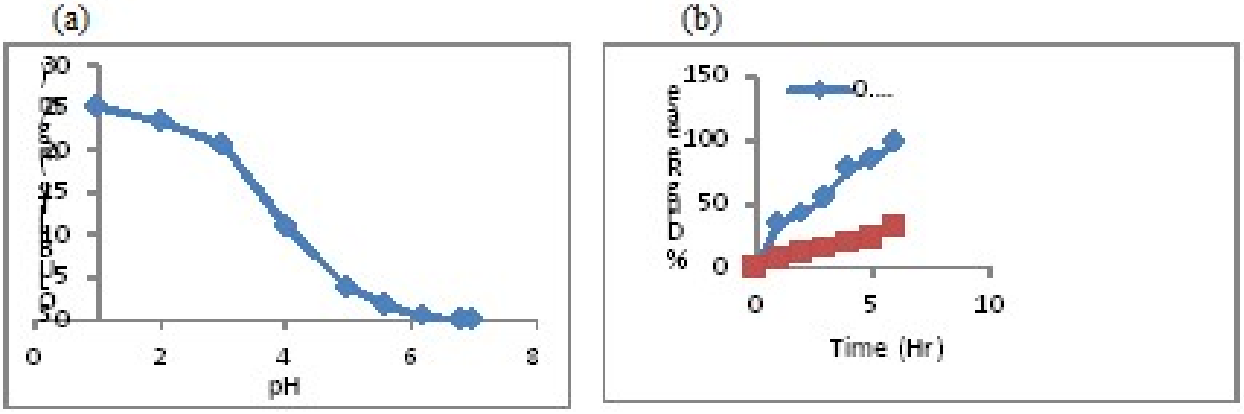

Fig. 2: (a) pH solubility profile of Ondansetron hydrochloric acid at 37^0C (b) pH dependent release of Ondansetron HCl from HPMC matrix device

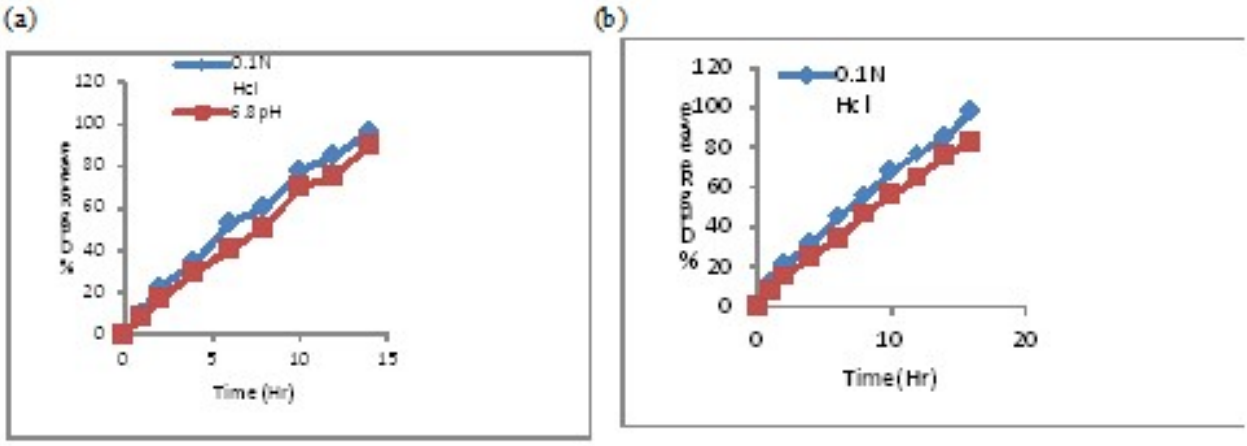

Fig. 3: (a) Effect of addition of citric acid and tartaric acid (b) on the release of Ondansetron hydrochloride from HPMC matrix.

The formulations containing EF1-EF7 by using Eudragit L100-55 in different concentrations to achieve pH independent drug release. From the above results out of all formulations the EF7 showed excellent dissolution profile and good correlation in both 0.1N and 6.8 pH buffer media and even the drug release was extended up to 22hrs fulfilling the objective of the work. More over enteric polymer have comparatively high molecular weight and show long residence within matrix gel layer facilitating their pH modulation to last longer than organic acids. In conclusion the combination anionic (Eudragit L100-55) and nonionic polymers (HPMC K100) to matrix tablets to achieve pH independent drug release.

Effect of surface pH of tablet

The determination of surface pH is one of the major parameter either the HPMC drug device is maintaining the constant surface acidic pH of the tablet in 6.8 phosphate buffer for prolonged time. For this study two techniques were used one is common technique to take 20

ml phosphate buffer in a Petri dish and tablet was immersed in the Petri plate at the surface of tablet dipped pH electrode and it will show the surface pH of the tablet. The optimized formula containing Eudragit L100-55 was found for prolonged drug release time acidic pH was maintained at the surface of the tablet (A Strebel *et al* (2000).

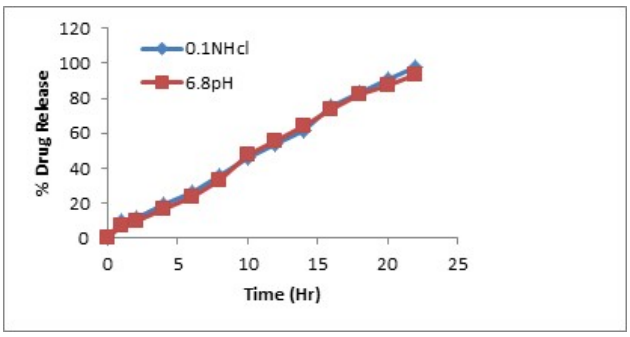

Fig. 4: Effect of the addition of Eudragit L100-55 on the release of Ondansetron hydrochloride from HPMC matrix

Comparison of release profile with pH modulating agent and Eudragit L100-55

The method of preparation of tablets with pH modulating agent has selected wet granulation, and direct compression methods. In comparison direct compression method was found good physical character of the tablets than wet granulation, because of very sticky granules, degradation of drug and color change after formation of tablets. In case of Eudragit L100-55, solid dispersion technique was adopted for mixing both the drug and polymer, applied direct compression and wet granulation approach. In the solid dispersion method, the yield was very low due to its sticky nature and it took more time to get dispersion completely dried. The direct compression failed to obtain desirable results where as wet granulation considered best in tablet ting properties. Moreover, as these enteric polymers have comparatively high molecular weights, they show longer residence time within the matrix gel layer, to prolong their pH modulation effect to last longer compare with 'smaller molecular weight' acids such as citric acid, tartaric acid.

Kinetics and mechanism of drug release

To study the release kinetics, data obtained from the in-vitro drug release mechanism studies were plotted in various kinetic models such as zero order, first order, Higuchi and Pappas equations, to know the mechanism of drug release and to compare the differences in the release profile with pH modulating agents and without pH modulating agents of HPMC based matrix tablets. The incorporation of pH modifiers resulted in an anomalous release, the control formulation produced n value 1.3275, corresponding to a zero order release mechanism (Siepmann J *et al,* 2000), Higuchi T1963, Peppas NA 1985). In the case of citric acid, tartaric acid with increasing pH modifier concentration the slope (n) tended to decrease, whereas constant (k) increased, suggesting that higher acid concentrations increased drug diffusibility.

CONCLUSION

This study has demonstrated the influence of pH on the gel layer behavior of the drug release characteristics of nonionic and anionic hydrophilic/enteric matrices. The addition of 10% w/w citric acid and 7.5% tartaric acid to matrices of various polymers showed pH independent release. However, the most efficient and pH independent release has shown by HPMC with Eudragit L100-55 polymer matrices. Whereas, the addition of Eudragit L100-55 polymer and HPMC based matrix tablets maintain low pH value within the tablet during prolong period. Through this approach, it is promising to design a pH independent once daily (Gopi Venkatesh *et .al*, 2011)) control release Ondansetron HCl for the treatment of chemotherapy induced nausea vomiting and post operation induced vomiting. Then values of correlation coefficients were also determined using DD Solver (Microsoft Excel Version).

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REFERENCES

Antonarakis ES and Hain RD (2004). Nausea and vomiting associated with cancer chemotherapy: drug management in theory and in practice. Arch Dis Child., **89**(9): 877-880.

Chatterjee S, Rudra A and Sengupta S (2011). Current concepts in the management of postoperative nausea and vomiting. *Anesthesiol. Res. Pract.,* **2011**: 748031.

Daisy chella kumari,S S Vengatesh, K Elango, R Devi Damayanthi, N Deattu and P Christina (2012). Formulation and Evaluation of Floating tablets of Ondansetron Hydrochloride. *Int. J. Drug Dev. & Res.*, **4**(4): 265-274.

Gopi Venkatesh *et al*. (2011) .Modified release once daily dosage forms of ondansetron HCl using Diffucaps a technology.www.ondrugdelivery.com.

Hain RDW (2013). Nausea and vomiting associated with cancer chemotherapy, Drug therapy in theory and in practice. group.bmj.com

Haresh T Mulani and Nehal J Shah. (2011) Formulation development and *in vitro* evaluation of pH-independent sustained release matrix tablets of propranolol hydrochloride from HPMC based matrices using organic acids. *JITPS,* **2**(2): 46-58.

Higuchi T (1963). Mechanism of sustained action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J. Pharm. Sci.*, **52**(12): 1145-1149.

Kenny GN (2009). Risk factors for postoperative nausea and vomiting. *Anaesthesia*, **49**(supply): 6-10.

Manthena VS Varma, Aditya M Kaushal, Sanjay Garg (2005). Influence of micro environmental pH on the gel layer behavior and release of a basic drug from various hydrophilic matrices. *Journal of Controlled Release*, **103**: 499-510.

Paul J and Hesketh MD (2008). Drug Therapy in Chemotherapy-i., nduced Nausea and Vomiting. *Eng. Med*., **358**: 2482-2494.

Peppas N. A (1985). Analysis of Fickian and Non-Fickian drug release from polymers. *Pharm. Acta*. *Helv.,* **60**: 110-111.

Reza Fathi, Gilead Raday, Patrick Gosselin and Guy Goldberg (2014). Antiemetic extended release solid dosage form. US patent US 20140271851 A1.

Kalaichelvi R, Rao Bm, Manikanta S, Gopinath G, Usha M, Ramana Dv, Rao Ds And Jayachandran E (2012). UV spectrophotometric method for determination of ondansetron hydrochloride in pure and its formulation. Int. J. Pharm. Pharm. Sci., 4(Suppl 4): 151-152.

Smith A A, Kottai Muthu A, Wagh Bhushan Pandit Rao and R Manavalan (2009). Formulation development and evaluation of ondansetron hydrochloride sustained release matrix tablets. *J. Pharm. Sci. Res.*, **1**(4): 48-54.

Strebel A, J Siepmann, A Dashevsky and R Bodmeier (2000). pH-independent release of a weakly basic drug from water-insoluble and soluble matrix tablets. *J. Cont. Rel.*, **67**: 101-110.

Samuel R. Pygall, Sarah Kujawinski, Peter Timmins, Colin D Melia (2009). Mechanisms of drug release in citrate buffered HPMC matrices. *Int. J. Pharm.*, **370**: 110-120.

Sekar Rajan, Socorriana Coalco, Ramesh N Subramania Naiar Meyyanathan, Elango K and Bhojraj Suresh (2013). Once daily sustained release tablets of Ondansetron, a novel anti emetic. *Am. J. Pharmatech Res.*, **3**(2).

Siepmann J, Kranz H, Peppas NA and Bodmeier R (2000). Calculation of the required size and shape of hydroxypropyl methylcellulose matrices to achieve desired drug release profiles. *Int. J. Pharm*., **201**: 151-164.

Venkatesh, Gopi, M Vandalia, Lai, Jin-wang Springboro, Vyas, Nehal and H Yardley (2006). pH dependent control release weakly basic ondansetron HCl formulations. U.S. patent 60/762,750.

Vikrant K Nikam and Eudragit (2011). A versatile polymer. *Pharmacology Online,* **1**: 152-164.