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Influence of Kollidon SR on Ondansetron HCl pH Independent Drug Release from Hydroxypropyl Methyl Cellulose Matrix Tablets

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Abstract

The Polymers are tools used in novel drug delivery system to modify the drug release of pharmaceutical dosage form. Ondansetron HCl is a weakly basic drug belongs to BCS class-II; it is showing distinct pH dependent solubility. The major intention of the current study was to develop a pH independent controlled released system for pH dependent poorly soluble Ondansetron HCl. The effect of combination of polymers on parameters like release pattern, release mechanism of the drug were studied. A 3^2 full factorial design was used to study the effect of Kollidon SR on Ondansetron HCl Drug Release from Hydroxypropyl Methyl Cellulose Matrix Tablets. The release rate from formulated matrix tablets was studied at both SGF (pH 1.2) and SIF (pH 6.8). Drug release from Kollidon SR and Methocel (1:1) based matrix system based tablets was found to pH independent controlled drug release up to 24h with >90% drug release. Kollidon SR has a distinctive character of maintaining tablets geometric shape until the end of dissolution test, this is mainly due to the water insoluble content, polyvinyl acetate, forming 80% (w/w) of Kollidon SR, while the remaining content 20% (w/w) is the water soluble, polyvinylpyrrolidone, responsible for pore formation causing a diffusion controlled release The similarities in Release profiles were evaluated by applying the model independent (f2) similarity factor. The Optimized formulation characterized by DSE, X-RD and FT-IR studies was found not having any interaction with polymer and drug. The Optimized Formulation followed zero order with non-Fickian diffusion method. In conclusion, Kollidon SR and Methocel k100 were found to be novel potential candidates for the development of pH independent controlled delivery system of Ondansetron HCl.

Keywords: *Ondansetron hydrochloric acid; pH independent controlled drug delivery system, Kollidon® SR, METHOCEL K100M*

INTRODUCTION

The oral drug delivery is by far the most preferable route of drug delivery system, due to ease of administration, patient compliance and flexibility in formulation. Most of the active pharmaceutical ingredients are weak acids And weak bases these salts showed variable drug release pattern in different areas of GIT, weakly basic drugs are highly soluble in acidic pH and the solubility was reduced to increase the pH shift to the intestinal pH 6.8 Phosphate medium, due to pH dependent solubility, such a type of drugs is not easy to formulate a controlled release dosage form to the formulator [1]. Ondansetron hydrochloride is a serotonin sub type-3 (5-hydroxytryptamine-3) receptor antagonist [2]. 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. The solubility it exhibit high in stomach at low pH (pH 1.2) at 37^0C (23mg/ml) and at higher pH (6.8 pH phosphate buffer) it exhibits poor solubility (0.036 mg/ml) and precipitation of drug was found. It indicates incomplete results, irregular drug absorption and fluctuations in plasma concentrations. It causes either it will not reach therapeutic levels or it may leads to toxic levels. pH independent controlled released matrix tablets is a special type of controlled release drug delivery system. The convenience of obtainable literature indicate that a number of methods have been attempt to developed pH-independent controlled drug release [3]. away 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 [4]. And another technique was developed pH adjuster such as organic acids this technique was somewhat better but the formulator was observed some manufacturing defects and prolonged drug release is very difficult [5-6].

Hydrophilic polymers were chosen because of its controlled release a well as good pH independent release polymer [9]. The pH independent swelling of HPMC is attributable to the constant drug release in entire pH of GIT [10]. Kollidon SR it is a convincing polymer is expected to be easily applicable for pH independent controlled released matrix tablets by direct compressible method [11].The present investigation is aimed to develop a pH-independent control drug release dosage form of by using Kollidon® SR 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 [12]. The Kollidon SR is a potentially useful novel excipient for the production of pH-independent extended release matrix tablets. It will be useful for all the pH-dependent soluble drugs. The objective of the present investigation was to study the effect of various polymers and their Concentration on the drug release characteristics, pH independent drug release, and other physicochemical properties of the tablet dosage form. Ondansetron was used as the model drug to study the release characteristics of the formulated tablet dosage form as it is pH dependent soluble drug. The recommended oral dose regimen of Ondansetron hydrochloride is 8 mg, three times a day. The dose of Ondansetron hydrochloride should be flexible in the range of 8-32 mg a day. The selection of dose regimen should be determined by the severity of the Emetogenic. The present study was undertaken to once daily pH independent controlled released matrix tablets and to check the Influence of variation in the concentration of different polymers on the release rate of the drug and the physicochemical properties of the dosage form.

MATERIALS AND METHODS

Ondansetron HCl was obtained from Pranami Drugs Pvt. Ltd., Gujarath, Hydroxy Propyl Methyl Cellulose (Methocel K100M), Kollidon SR were supplied by Yarrow chemicals , Mumbai, India, AVICEL PH 101 was procured from Qualigens Fine Chemicals Lactose and Magnesium Stearate obtained from Aman chemicals(Vijayawada, AP), respectively

Preparation of Ondansetron HCl Matrix Tablets

All the tablet formulations with different drug and polymer ratios were prepared by direct compression method. Kollidon® SR and Methocel k100M was chosen, for its

pH independent controlled released property. controlled release matrix tablets were prepared by direct compression method as per the formula given in the Table 1 .Initially the drug was passed through sieve no #30, different polymer concentrations passed sieve no #40 ,Avicel PH 101,lactose and magnesium stearate , talk. These powders were mixed until a homogenous mixture was obtained. Ondansetron and all other ingredients were exactly weighed and sifted through sieve no# 40. The materials were mixed and blended in a mortar. Finally the blend was compressed 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). With average weight of the Tablet is 300mg.physicochemical properties for various parameters were evaluated for prepared tablets. (table.1)

Selection of experimental design

A 3^2 factorial design was selected for the study. Two main factors *i.e.* combination of the polymer and ratio were evaluated at different concentrations. Three levels of the factor X1 (concentration of HPMC K100M) and X2 (Kollidon SR) selected to find out its effect on drug release. While ratios of polymers at three levels were selected to identify separate as well as combined effects of both controlled released polymers (HPMCK100M) . Percentage of drug release after 2 h (>20%) and percentage of drug release after 20 h (<90%) were selected as dependent variables. In this design, two factors were studied at three levels and experimental trials were performed at all nine possible combinations.Composition of the 3^2 full factorial design investigated is shown in (Table 2).

Table 1: *Priliminary Formulations of Ondansetron without pH modulating agents.*

INGREDIENTS	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**
Ondansetron HCl	25	25	25	25	25	25	25	25
Methocel K100M	25	50	75	100	-	-	-	-
Kollidon Sr	-	-	-	-	25	50	75	100
PVP	3	3	3	3	3	3	3	3
Avicel PH102	236	211	186	161	236	211	186	161
Megnisium Stearate	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6
Total (Mg)	300	300	300	300	300	300	300	300

Table 2: *3^2 full factorial design.*

Formulation code	Coded values	
	X_1	X_2
F1	-1	-1
F2	-1	0
F3	-1	1
F4	0	-1
F5	0	0
F6	0	1
F7	1	-1
F8	1	0
F9	1	1

Translations of coded values to actual values			
Coded values	-1	0	1
Methocel k100m	25	50	75
Kollidon SR	25	50	75

Angle of Repose
Angle of repose was determined for the powder blend as in indicator for favorability characteristic. Based on flow of the powder the method was selected for tablet preparation. This was determined by a simple fixed funnel method the blend was poured through a dry funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap(r) was measured and angle of repose was calculated by using the formula [13].

Hardness Test
The hardness of matrix tablets was determined using Pfizer hardness tester. From each formulation batch three matrix-tablets were randomly taken and the values were calculated.

Friability Test
The test was performed by initially weighing 5-tablets and then transferring into VEEGO Friabilator. The friabilator was operated at 25 rpm for 100 revolutions and the matrix-tablets weighed again. Friability was computed as percent loss in weight.

Weight Variation Test
From each formulation batch ten matrix-tablets were randomly taken and weighed individually to determine variation.

Uniformity of Thickness
From each formulation batch, six matrix-tablets were randomly taken and measured for thickness using a micrometer screw gauge.

Drug Content Uniformity
For estimation of drug content first five tablets were taken and then crushed into fine powder in the mortar. Then this fine powder equivalent to 25 mg of Ondansetron HCl was extracted in pH 6.8.phosphate buffer. This sample was filtered through a Millipore filter of 0.45 µm pore size. After suitable dilutions drug content was Spectrophotometry determined at a wavelength of 249 nm. [15].

Dissolution Studies
The *in-vitro* drug release study was carried out by using USP Type–II, rotating paddle apparatus (VEEGO Instruments Corporation, Mumbai, India). The operating speed was at 50 rpm. SGF (pH1.2, 900 ml) was used as dissolution medium. The temperature was maintained at 37 ± 0.5^{0}C. Simultaneously we studied both pH 1.2 and 6.8 continuously for complete drug release study. Samples were withdrawn at pre-determined time intervals, filtered and analyzed by using UV-Visible Spectrophotometer (ELICO SL-210) at 249 nm [12].

Similarity factor analysis
The dissolution profiles of the formulated Dipyridamol tablets were compared with both medium pH 1.2 and pH 6.8 phosphate buffer and evaluate pH-independent release pattern of dipyridomol from the optimized tablets in the release media of pH 1.2 and pH 6.8.Similarity (*f2*), factors are using a similarity factor described in the following equation:

$f2 = 50 \times \log \{[1+ (1/n) Rj-Tj\ nj=1^{2}]^{-\circ\cdot5}\times100\}$

The Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA) suggested that two dissolution profiles can be declared similar if *f2* is between 50 and 100 [8].

***In- Vitro* Drug Release (Mechanism)**:
To know the mechanism of drug release from all these formulations, the data to be fixed to zero order (cumulative amount of drug released vs. time), first-order (log cumulative percentage of drug remaining vs. time), Higuchi's (cumulative percentage of drug released vs square root of time), and Korsmeyer's (log cumulative percentage of drug released vs. log time)

plotted and regression values were calculated [11].

Scanning Electron Microscopy Studies

The Scanning electron microscopy studies were used to examine the solid state physical structure of the prepared precipitated form of the powder and pure ondansetron HCl. S.E.M. photographs of Ondansetron HCl, its physical mixture with different pH medium were obtained using a scanning electron microscope (JEOL JSM 5600) with accelerating voltage from 0.5 to 30 KV.

RESULTS AND DISCUSSION

pH-Dependent solubility Of Weakly Basic Drug

Solubility of ondansetron HCl was carried out in both mediums 0.1N HCl and 6.8 phosphate buffer .the solubility of ondansetron in 0.1N HCl was found to be 23.3 mg/ml. The solubility of Ondansetron HCl in pH 6.8 phosphate buffer was 0.036mg/ml and the drug was immediately precipitated it formed large crystal shown in (Fig: 1). The solubility studies was revealed Ondansetron HCl is a completely pH dependent soluble drug. Hence in this investigation an attempt was made to develop a suitable pH independent controlled released matrix tablets of Ondansetron HCl.

Figure 1: *Laboratory Comparison of solubility (Ondansetron HCl) both acidic and basic medium.*

FT-IR Studies

The FT-IR of Ondansetron HCl and polymer mixtures and optimized matrix tablets dosage form studied by kbr pellet technique. The Ondansetron HCl exhibited characteristic peaks at 3,394 and 1,633 cm, attributed to O-H stretching and C=O stretching vibrations. The physical sprectrum not showed significant shift in peaks of Ondansetron HCl and somewhat changed some intensity peaks were found. And as well as optimized formulation of Kollidon SR with Methocel K100M formulation were studied the band at 3,499 cm for O-H stretching and 1,699 cm for C=O Stretching were found. The results of IR spectroscopy reveal that there was no chemical interaction between Ondansetron and Kollidon SR with Methocel K100M combination of polymers.IR sprectra shown in (Fig no: 2, 3).

Table 3: *FTIR Spectral studies.*

Functional Groups	Ondansetron HCl
N- CH_3 streching	3200 – 3180
C=O acid Stretching	1635 – 1612
C-H alkane stretching	2720 – 2662
Aromatic stretching	750 – 772

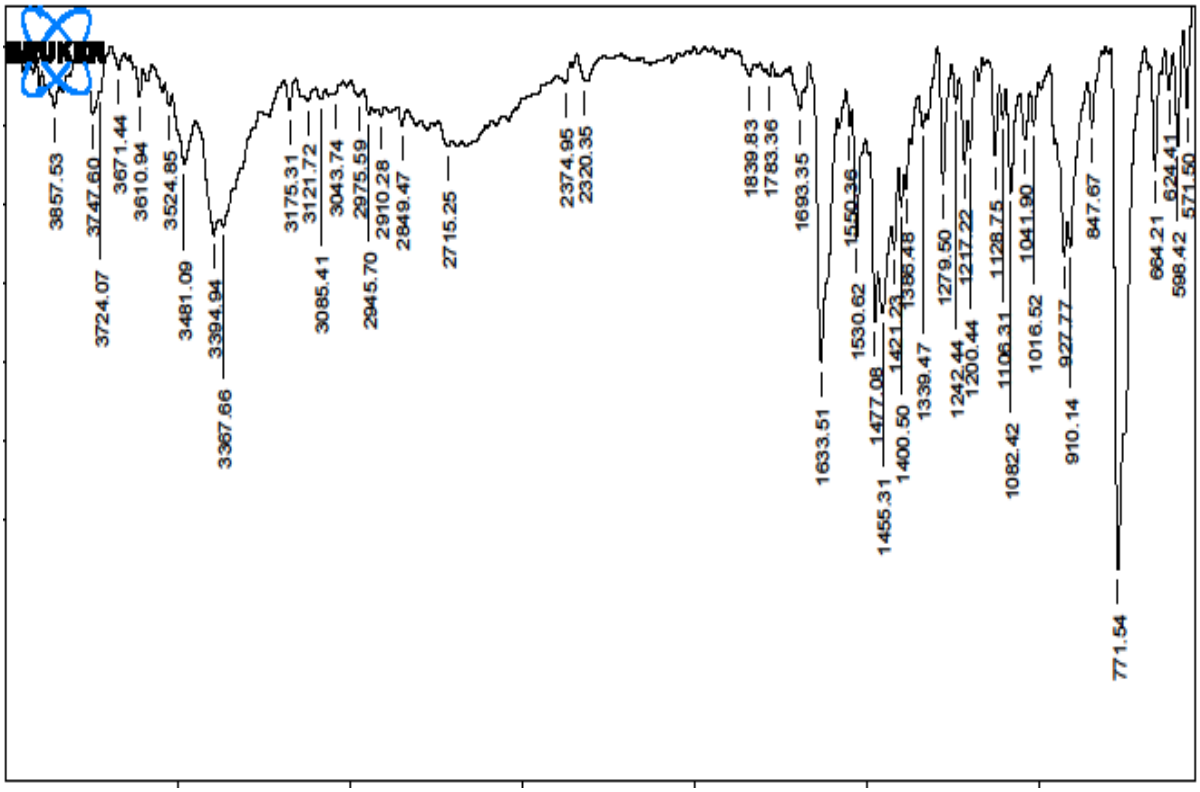


Figure 2: *IR Spectra of Ondansetron.*

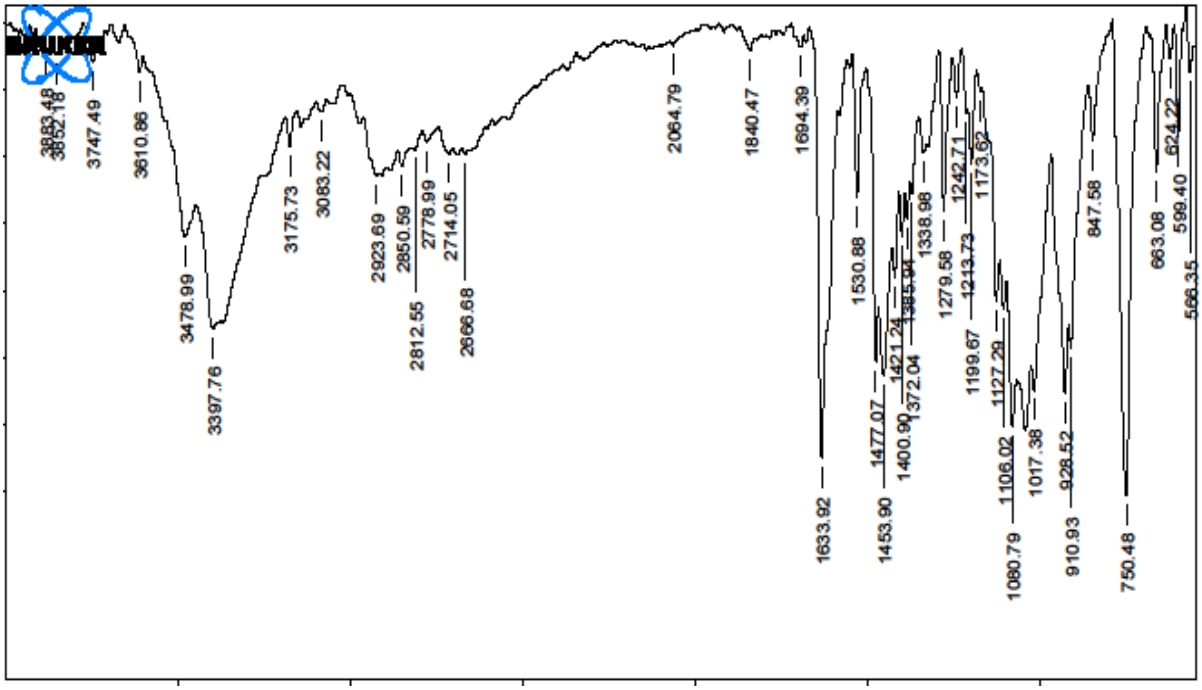
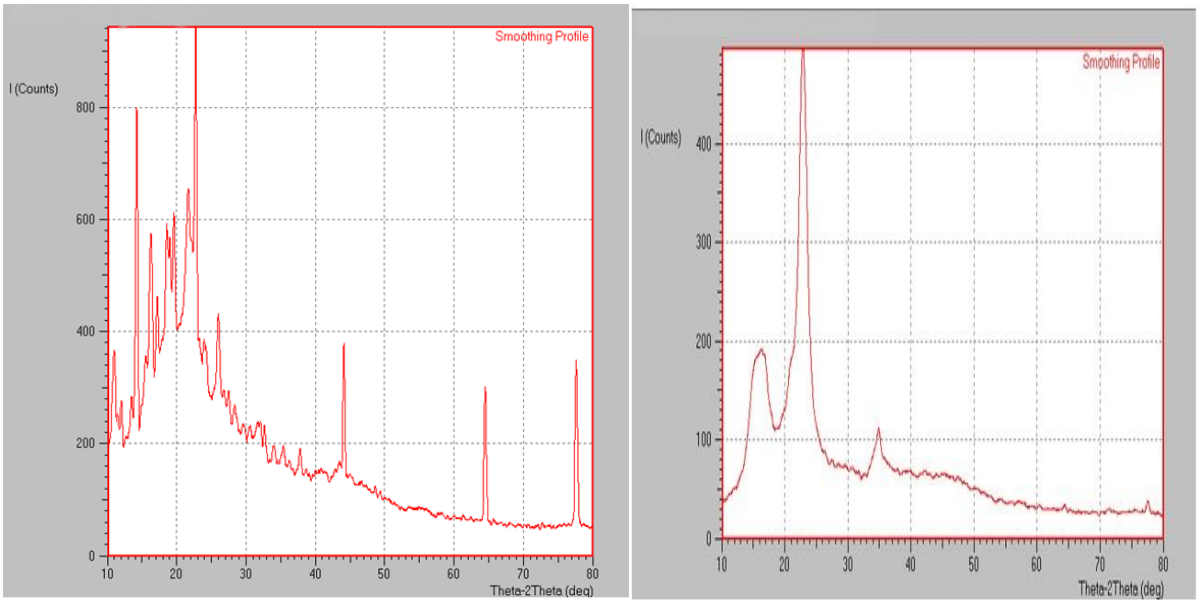


Figure 3: *IR Spectra of Ondansetron HCl with HPMC K100+KOLLIDONE SR.*

XRD Analysis

XRD (X-Ray diffraction) the freshly prepared powdered samples under controlled temperature and humidity conditions were record at room temperature on X-Ray diffract meter with Cu Ka radiation (1.54 Å), at 40 kV, 30 mA, passing through a nickel filter with a divergence slit (0.5°), anti-scattering slit (0.5°), and receiving slit (1 mm). The presence of many diverse peaks in the X-ray diffraction pattern indicate that Ondensetron HCl API crystalline material with characteristic diffraction peaks appearing at a diffraction angle of 2θ at 10.2, 19.2, 22.5, 29.11 & 35.6. The Optimized formulation containing Methocel k100M with koliidon SR exhibits a distinct pattern with diffraction peaks at diffraction angle of 2θ at 7.82, 15.99 and 22.5. The diffraction pattern of placebo was found to differ in comparison with drug. Some peaks were disappeared, some peaks were appeared & some peaks heights were decreased. taken as a whole diffraction pattern revealed that there is no change in polymorphic properties of the drug and the drug is well distributed throughout the preparation of optimized formulation(F9) XRD results was shown in (Fig 4).

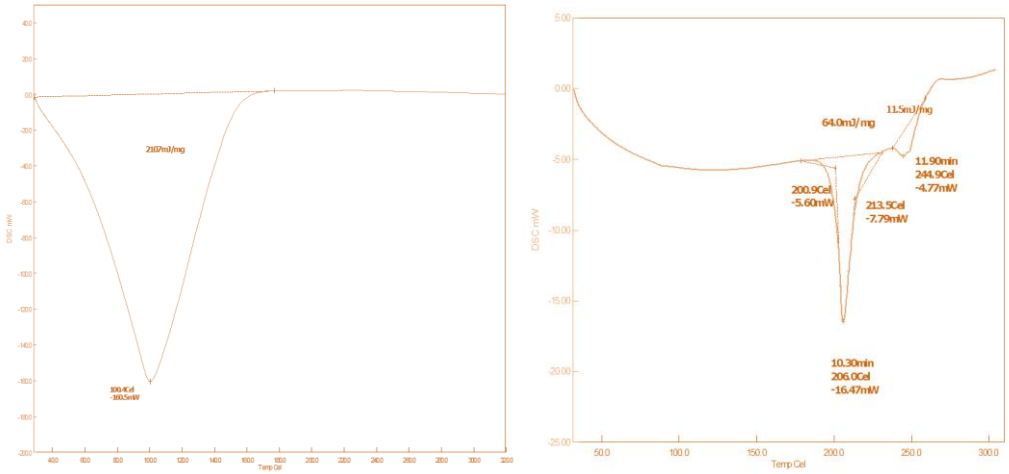


a) **b)**

Figure 4: *(a) X-ray diffraction spectra of pure Ondansetron HCl (b) X-ray diffraction spectra of precipitated powder Ondansetron HCl in 6.8 Phosphate buffer.*

DSC Study

DSC study was performing on the pure ondansetron HCl, and optimisized formulation with Methocel k100 and Kollidon SR used in the study. The drug: polymer complex to access whether there is any interaction between drug and polymer. The thermo gram of pure Ondansetron gave a melting endotherm at 203.25ºC. The thermo gram of optimized formulation gave the same melting endoderm 213 25ºC. So from the DSC curve it has been confirmed that there is no change in endothermic peak of the drug. And hence the drug and polymers are well compatible with each other. [16]. DSC of spectrum was shown in (Fig 5).



a) **b)**

Figure 5: *(A) DSC thermo gram of pure ondansetron HCl (B). DSC thermo gram of precipitated powder ondansetron HCl in 6.8 Phosphate buffer*

Pre-compression evaluation for formulated of the Powder Mixture:

Prior to compression, all the formulations were evaluated for their flow property. From the values of Angle of repose, it is clear that blends having Kollidon SR formulation is showed better flow properties than Methocel K100M. The formulation containing (F1-F4) property was falling in the passable range (31.32±0.12) and Kollidon SR (F6-F9), flow property was falling in the excellent, in which values of angle of repose were found to be and 18.12±0.32 respectively, While formulation with Kollidon® SR with Methocel k100 (F9) had good flow property, The values of angle of repose were 24.23±0.32and 23.45_± 0.19 respectively. The Bulk densities of the powder blends of all the formulations ranged from 0.331 to 0.521 g/cc and tapped densities of the powder blends of all the formulations ranged from 0.444 to 0.842 g/cc. The Hausners ratio values ranged from 1.34 to 1.66. Evaluated values were less than 1.25 indicating good flow. It means that the powder flow properties were within the pharmacopoeias limits. The Carr's index values ranged from 18 to 35%. High compressibility is required for Kollidon SR when compared to Methocel k100. The results obtained indicates that the powder flow properties were within the pharmacopoeias limits, the Kollidon SR polymer was found excellent flow property.(Table 4).

Table 4: *Pre-compression Parameters of the Powder Mixture.*

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose
F1	0.337±0.031	0.444±0.001	25.45	1.34	31.32±0.12
F2	0.347±0.011	0.424±0.006	18.16	1.22	25.21±0.32
F3	0.346±0.021	0.458±0.009	24.45	1.32	29.45±0.24
F4	0.356±0.021	0.468±0.012	23.93	1.31	30.23±0.17
F5	0.501±0.009	0.833±0.0023	39.85	1.66	19.32±0.32
F6	0.511±0.008	0.823±0.006	37.91	1.61	18.12±0.32
F7	0.521±0.011	0.842±0.007	38.12	1.61	20.12±0.32
F8	0.515±0.007	0.822±0.008	37.34	1.59	20.54±0.12
F9	0.508±0.006	0.811±0.009	37.36	1.59	24.23±0.32

Table 5: *Post-compression Parameters of the controlled released matrix tablets.*

Tablets	Average weight,(mg)	Thickness,(mm)	Hardness	Friability	Drug content%
F1	301±2	4.85 (0.008)	6.23 ±0.29	1.01 (0.51)	98.56 (2.12)
F2	298±1	4.87 (0.006)	6.42 ±0.34	0.56 (0.11)	101.12 (1.23)
F3	301±3	4.89 (0.005)	5.98 ±0.29	0.67 (0.21)	102.12 (3.12)
F4	300±2	4.86 (0.009)	5.91 ±0.44	0.54 (0.52)	100.10 (4.2)
F5	299±2	4.85 (0.004)	6.72 ±0.54	0.76 (0.20)	98.12 (5.2)
F6	304±1	4.84 (0.009)	6.65 ±0.34	0.85 (0.08)	101.12 (4.3)
F7	302±3	4.86 (0.008)	6.98 ±0.34	0.87 (0.22)	103.23 (3.8)
F8	303±2	4.87 (0.005)	6.54 ±0.64	0.96 (0.07)	101.29 (2.3)
F9	299±1	4.83 (0.005)	6.75 ±0.34	0.45 (0.31)	97.23 (5.2)
F10	301±2	4.87 (0.007)	6.43 ±0.24	0.48 (0.41)	100.12 (4.5)

Post-compression evaluation for formulated matrix tablets*:*

The weight of the tablet varied between 295 mg to 300 mg for different formulations with low standard deviation values, indicating uniformity of weight. The variation in weight was within the range of ±5% complying with pharmacopoeia specifications. The hardness for different formulations was found to be between 5 to 6.5 kg/cm^2 indicating satisfactory mechanical strength. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. All the tablet formulations showed acceptable pharmacopoeias limits, the result are presented in (Table 5).

***In-Vitro* Drug Release Studies:**

In-vitro dissolution studies for all formulations were performed using the two–step dissolution method, in vitro dissolution studies were performed in both pH 1.2 and ph 6.8 buffers individually and by changing the pH, which better corresponds to real conditions in the gastro intestinal tract 2h in pH 1.2 and following in pH6.8 mediums, to see the effect of change in the pH of the dissolution medium on drug release. Results obtained in the *in vitro* drug release study of different formulations. A remarkable difference in the drug release from one polymer to another polymer formulations. From that Methocel k100M and Kollidon® SR at different proportions of drug and polymer ratios. The drug release was observed in pH 1.2 SGF and pH 6.8 phosphate buffer. The drug release from the matrix tablet in pH 1.2 was relatively faster from all the formulations but it was variable from polymer to polymer drug release in pH 6.8 phosphate buffer. when formulation containing with optimized concentration of Methocel K100M (P4,1:4 ratio), approximately 22.24% in pH 1.2 after 2h and 64% of drug release in 6.8 phosphate buffer after 24h respectively, It was Showed incompletely drug release and drug was not released complete from matrix device pH dependent drug release was found the drug released . However, in case of Kollidon SR(P8,1:4).the drug release was found approximately 57.24% in pH 1.2 after 2h and 96% of drug release in 6.8 phosphate buffer after 6h respectively, polymeric matrices showed quite a faster release in both pH 1.2 after 2h and 6.8 phosphate buffer with Kollidon SR ,the main reason for this Kollidon SR containing the water insoluble part; polyvinyl acetate, forming 80% (w/w) that maintains tablet shape and controlled the drug release, while the remaining part 20% (w/w) is the water soluble, Polyvinylpyrrolidone that dissolve in water exit open pores inside which water access from matrix device to dissolve the drug causing a diffusion controlled release mechanism [16]. It was found that Kollidon SR is enhancing the drug release in pH 6.8 phosphate buffer but drug release is not controlling in pH 1.2. the drug release need to controlled in pH 1.2 because ondansetron solubility was found it is highly soluble in pH 1.2, whereas another object drug release need to enhance in pH 6.8 phosphate due to pH

dependent solubility [19-21]. Shows a lower percent of drug release at pH 6.8 as compared to pH 1.2, high percentage of drug release in pH in pH 1.2 it was found pH dependent drug release of ondansetron with HPMC. Incase witth Kollidon SR polymer drug release was found drastic change was found, when concentration of kollidon sr was increased drug release was enhencced in both pH drug release was not controlled shown in (Fig.no 6).

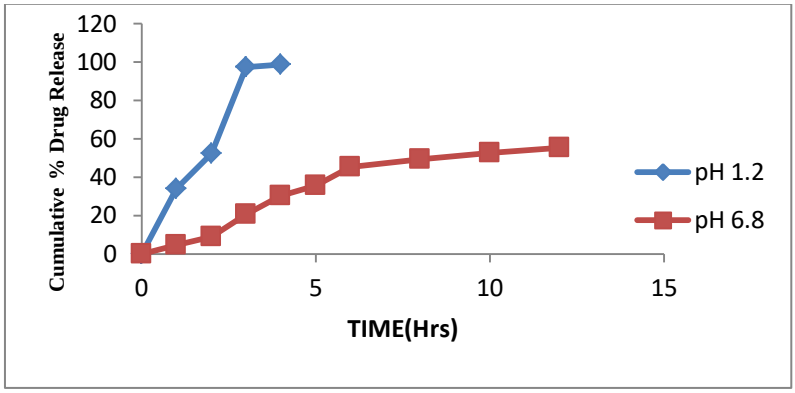


Figure 6: *Dissolution Profile of formulation with HPMC both pH 1.2 and 6.8 Phosphates Buffer.*

Optimization of Ondansetron HCl pH independent drug Release from the Prepared matrix Tablets:

A summary of various dissolution parameters calculated for the entire batch, a significant fraction of the drug remained unreleased amount from the tablets without Kollidon® SR. Though the highest percentage of drug release among batches containing combination of both Methocel K100 with Kollidon® SR approximately 22.24% in pH 1.2 the drug release was controlled and 96% of drug release at the end of 24h in both pH mediums respectively, it was clear that drug release was enhenced In pH 6.8 by influencing kollidon sr, the comparative analysis that combination of Methocel k100M with Kollidon SR improved drug release significantly. As the concentration of Kollidon SR increased, rate of drug release enhenced in pH 6.8 phosphate buffer. The main reason for this kollidon SR is having 20% polyvinyl pyrolidine it controlled saturation of drug and enhancing drug release, and Methocel k100M is controlling the drug release with their high viscosity nature. The combination of Methocel and Kollidon® SR (F5)was found pH independent drug release for extended up to 24h. The similarity of drug releas drug release in both pH was shown in (Fig.8).

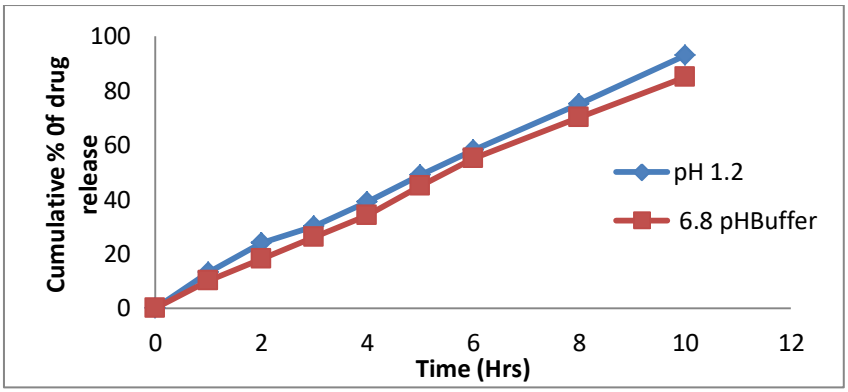


Figure 7: *Effect of pH on in vitro drug release profile of optimised Ondansetron pH independent control release tablet (F-5).*

Optimization data analysis

In order to find out optimized batch based on set criteria, 3^2 full factorial designs were applied. From the data obtained for factorial batches, ANOVA was performed to evaluate responses by a statistical model incorporating polynomial and interactive terms: The combination of Methocel and Kollidon® SR Matrix system optimized formulation had similar dissolution profile in both 6.8 phosphate buffer and pH 1.2 to each other (f2 >50) showing pH independent drug release of ondansetron HCl from the tablet .

$Y = \beta0 + \beta1X1 + \beta2X2 + \beta3X3 + \beta12X1X2 + \beta23X2X3 + \beta31X3X1 + \beta123X1X2\ X3$

The *in vitro* release data plotted different drug release graphs from all the formulations could be best expressed by Higuchi's Equation, as the coefficient values showed high linearity with R2 values between 0.958 to 0.991. It indicating that diffusion mechanism involved in the release of the drug from the tablets it proves the diffusion mechanism; the data were fit in to Korsmeyer Peppas Eqn. From the slope 'n' values ranging from 0.527 to 0.715, the diffusion mechanism involved in formulations was considered to be non-Fickian. [22-23]. When compared to all the nine formulations, formulation F-5 Methocel k100M:Kollidon SR in 1:1 ratio released 96.21% of Ondansetro HCl in 24h was selected as the optimized formulations. the optimized formulation followed zero order release kinetics with diffusive mechanism by non-Fickian (Table.6).

Table 6: *Drug Release kinetics of Formulated Matrix Tablets.*

Formulation code	Zero order plots Regression coeffient(R) st order plots	First order plots Regression coeffient(R)st order plots	Highuchi'plots Regression coeffient(R)	Korsmeyer'plot	
				Regression coeffient(R)	Slope (n)
F1	0.976	0.864	0.991	0.992	0.555
F2	0.989	0.961	0.986	0.997	0.549
F3	0.997	0.919	0.959	0.987	0.638
F4	0.986	0.854	0.989	0.978	0.528
F5	0.975	0.867	0.963	0.979	0.627
F6	0.984	0.929	0.979	0.976	0.704
F7	0.980	0.936	0.975	0.963	0.715
F8	0.996	0.879	0.987	0.971	0.542
F9	0.988	0.936	0.995	0.991	0.564

CONCLUSION

In present investigation effect of Kollidon SR and their combination on drug release kinetics was studied using 3^2 factorial design .the investigations concluded that combination of kollidon sr and Methocel k100 containing weakly basic Ondansetron HCl improved release kinetics of the drug . Thus to avoid precipitation out of pH dependent weakly basic drugs these technique is useful for pH independent controlled released system. It was concluded that Kollidon® SR is a potentially useful polymer for the production of pH-independent controlled release matrix tablets.

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