DEVELOPMENT AND CHARACTRIZATION OF GRANISETRON FAST DISSOLVING TABLETS

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ABSTRACT

The aim of work is to characterization and evaluation of fast dissolving tablet of Granisetron hydrochloride using super disintegrates like crosscarmellose sodium and sodium starch glycolate. FTIR studies revealed that there was no physico-chemical interaction between granisetron and other excipients. Tablet containing sodium starch glycolate showed excellent disintegration time and drug release as compared to other formulations. Granisetron is a selective 5HT3 receptor antagonist, which may have beneficial therapeutic ef fects in the treatment of vomiting and nausea resulting from cancer therapy. In the present work fast dissolving tablets of Granisetron have been prepared by direct compression method. Formulations were evaluated for precompressional parameters such as angle of repose, % compressibility and Hausner's ratio. The prepared tablets were evaluated for post compressional parameters such as hardness, friability, thickness, invitro dispersion time, wetting time, and water absorption ratio. From this study it is concluded that fast dissolving tablets could be prepared by direct compression method using different superdisintegrants enhanced dissolution will lead to improved bioavailability, improved effectiveness of Granisetron.

Keywords: Granisetron, superdisintegrants, FTIR studies, direct compression technique, in-vitro drug release studies.

1.INTRODUCTION

The FDT technology, which makes tablets dissolve or disintegrate in the mouth without additional water intake. The FDT formulation is defined by the Food and Drug Administration (FDA) as "a solid dosage form containing medical substances whish disintegrates rapidly, usually within a seconds, when placed upon the tongue.[1] The basic approach in development of FDT is the use of superdisintegrants, which provide instantaneous disintegration of tablet after putting on tongue, their by release the drug in saliva [2].The fast dissolving tablets are rapidly dissolved or disintegrate by the use of superdisintegrants. Fast dissolution"""" or fast disintegration typically requires dissolution or disintegrationof a tablet within one minute[3.] Granisetron hydrochloride is a selective 5-HT_3 receptor antagonist, which may have beneficial therapeutic effects in the treatment of vomiting and nausea resulting from cancer therapy[4,5] Granisetron hydrochloride undergoes extensive hepatic first pass metabolism with a Bioavailability of 60%. The terminal elimination half-life is 3 to 14 hours after oral administration. Granisetron hydrochloride is about 65% bound to plasma proteins. In the present study, an attempt was made to develop

fast dispersible tablets of Granisetron Hydrochloride and to improve its bioavailability.[6] The objective of the present study is to develop fast dispersible tablets of Granisetron Hydrochloride and to study the effect of functionality differences of superdisintegrants on the tablet properties as well as to improve the patient compliance without compromising the therapeutic efficacy.

2. MATERIALS AND METHOD

2.1 MATERIALS

Ganisetron was collected as a gift sample from Reddy' laboratories, Hyderabad, super disintegrants and other excipients were purchased from AR chemicals.

2.2 METHODODOLOGY

FTIR studies [8]

The Fourier-transform infrared spectra of Granisetron hydrochloride and mixture granisetron hydrochloride with other excipients were obtained by using FTIR spectroscopy – 5300 (JASCO Japan). Samples were prepared by KBr pressed pellet technique. The scanning range was 400-4600 cm-1 and the resolution was 4 cm-1.

Formulations Table

Table-1: Formulation table

S.No	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Granisetron	2	2	2	2	2	2	2	2	2
2	Croscaramellose	5	7.5	10	-	-	-	-	-	-
3	Sodium starch glycolate	-	-	-	5	7.5	10	-	-	-
4	Avicel pH 101	-	-	-	-	-	-	5	7.5	10
5	Mannitol	90	87.5	85	90	87.5	85	90	87.5	85
6	Magnesium stearate	1	1	1	1	1	1	1	1	1

7	Talc	1	1	1	1	1	1	1	1	1
8	Aspartame	1	1	1	1	1	1	1	1	1
9	Total wt	100	100	100	100	100	100	100	100	100

Procedure

Direct compression technique[9]

Fast dissolving tablets of Granisetron were prepared by direct compression. Allthe ingredient s were passed through 40-mesh separately. Then the ingredients were weighed and mixed ing eometrical order and compressed into tablets of 100mg using 6mm round flat punches on 10 station rotary tablet machine (Rimek).

EVALUATION STUDIES[10,11]

Pre compression parameters

Bulk density: Apparent bulk density (ρb) was determined by placing presieved drug excipients blend into a graduated cylinder and measuring the volume (Vb) and weight (M) "as it is".

$$\rho b = M/Vb$$

Tapped density: The measuring cylinder containing a known mass of blend was tappedfor a fixed number of taps. The minimum volume (Vt) occupied in the cylinder and theweight (M) of the blend was measured. The tapped density (ρt) was calculated using following formula.

$$\rho t = M/ Vt$$

Angle of repose: Angle of repose (θ) was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height(h) was obtained. The radius of the heap (r) was measured and angle of repose wascalculated.

$$\theta = \tan\text{-}1\ h/r$$

Compressibility index: The simplest way of measurement of free flow property of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by % compressibility that is calculated as follows:

$$C = (\rho t - \rho b) / \rho t \times 100$$

ρt - Tapped density,

ρb - Untapped bulk density

ii) Post compression parameters[12,13]

Weight variation test:-The weight variation test was performed by selecting twenty tablets at random. The average weight of tablets was determined.

Hardness:- The tablet crushing strength was determined by using Pfizer hardness tester.The test was carried in triplicate for each batch.

Friability:- The friability of GRA tablets (n=10) was determined using Roche friabilator (scientific). The weight of dedusted tablets before and after test was determined to compute friability. The friability was determined as percentage weight loss of tablets from each batch.

The percentage friability was measured using the formula,

$$\% F = \{1-(Wo/W)\} \times 100$$

Where,

% F = friability in percentage

Wo = Initial weight of tablet

W = weight of tablets after revolution

Drug Content: The drug content was determined by triturating tablets (n=5) in a mortar and pestle. The powder equivalent to 2.24 mg of GRA was dissolved in distilled water. The solutionwas filtered through Whattmann filter paper no. 41. The filtrate was analyzed by U.V. spectrophotometer (Shimadzu 1700 PharmSpec) at 298 nm. The drug content in average weight of tablets was determined in triplicate.

Wettingtime: The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in a Petridish with a 10 cmdiameter. Ten millimeters of watercontaining Eosin, a water-soluble dye, is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

Waterabsorptionratio(%):A piece of tissue paper folded twice was placed in a small petridi sh (Internal Diameter = 6.5 cm) containing 6 ml of water. A tablet was placed on the paper an

d the time required for complete wetting was then measured. The water absorption ratio (R) was determined using the following Equation.

Water absorption ratio (R) = $\frac{W a - W b}{W b} \times 100$

Where,

Wb is the weight of the tablet before water absorption and

Wa is the weight of the tablet after water absorption

In Vitro Disintegration Test:-

The disintegration time of tablets was determined by using Disintegration test apparatus (V scientific). Tablets were placed in disintegration test assembly and disc was placed on tablets in each glass tube of assembly. The assembly was dipped in a vessel containing 900 ml distilled water at 37°C. The time for disappearance of tablet residue above mesh was noted as disintegration time.

Dissolution Study:- Dissolution studies were performed for optimum batches of GRA tablets using USP apparatus II and phosphate buffer I.P. pH 6.8 (500 ml, 37±0.5ºC) as dissolution medium stirred at 50 rpm. Aliquots of dissolution medium were withdrawn at intervals of 5 minutes and filtered through Whattmann filter paper no. 41. The absorbance of each sample was then measured at 298 nm by U.V. spectrophotometer and concentration was determined.

Drug release kinetics[14,15]

Zero order release kinetics

It refers to the process of constant drug release from a drug delivery device independent of the concentration. In its simplest form, zero order release can be represented as

$$Q = Q0 + K0\ t$$

Where Q is the amount of drug released or dissolved, Q0 is the initial amount of drug in solution (it is usually zero), and K0 is the zero order release constant.

First order release kinetics

The first order Equation describes the release from system where release rate is concentration dependent, expressed by the equation:

$$dC / dt = - Kt$$

Where K is first order rate constant expressed in units of time $-^{1}$.

This equation can be expressed as:

$$Log\ Ct = Log\ C0 – k\ t / 2.303$$

Where, C0 is the initial concentration of drug and Ct is the concentration of drug in solution at time t. The equation predicts a first order dependence on the concentration gradient (Co - Ct) between the static liquid layer next to the solid surface and the bulk liquid.

Higuchi Model

The first example of a mathematical model aimed to describe drug release from a matrix system was proposed by Higuchi in 1963 this model is applicable to study the release of water soluble and low soluble drugs incorporated in semisolid and solid matrices Model expression is given by the equation:

Q = A [D (2C - Cs) Cs t] 1/2

Where Q is the amount of drug released in time t per unit area A, C is the drug initial concentration, Cs is the drug solubility in the media and D is the diffusivity of the drug molecules (diffusion coefficient) in the matrix. Simplified Higuchi model describes the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Equation.

Q = KH t1/ 2

The data obtained were plotted as cumulative percentage drug release versus square root of time. The slope of the plot gives the Higuchi dissolution constant KH. 4. Korsmeyer - Peppas Model

Korsmeyer et al (1983) derived a simple relationship which described drug release from a polymeric system. Ritger and Peppas and Korsmeyer and Peppas developed an empirical equation to analyze both Fickian and non-Fickian release of drug from swelling as well as nonswelling polymeric delivery systems. To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer – Peppas model

$$Mt / M\alpha = K\, tn$$

Where Mt/Mα is fraction of drug released at time t, k is the rate constant (having units of tn) incorporating structural and geometric characteristics of the delivery system. n is the release exponent indicative of the mechanism of transport of drug through the polymer. The n value is used to characterize different release mechanisms.

Stability studies:-[16]The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile. The prepared tablets of Granisetron were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2^{o}c and refrigerator 2-8^{o}c for a period of 90 days.

3.RESULTS AND DISCUSSION

FT-IR Spectrum of Granisetron

FT-IR Spectra of Granisetron and F3 formulation were recorded. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Granisetron and polymer. It also confirmed that the stability of drug during microencapsulation process.

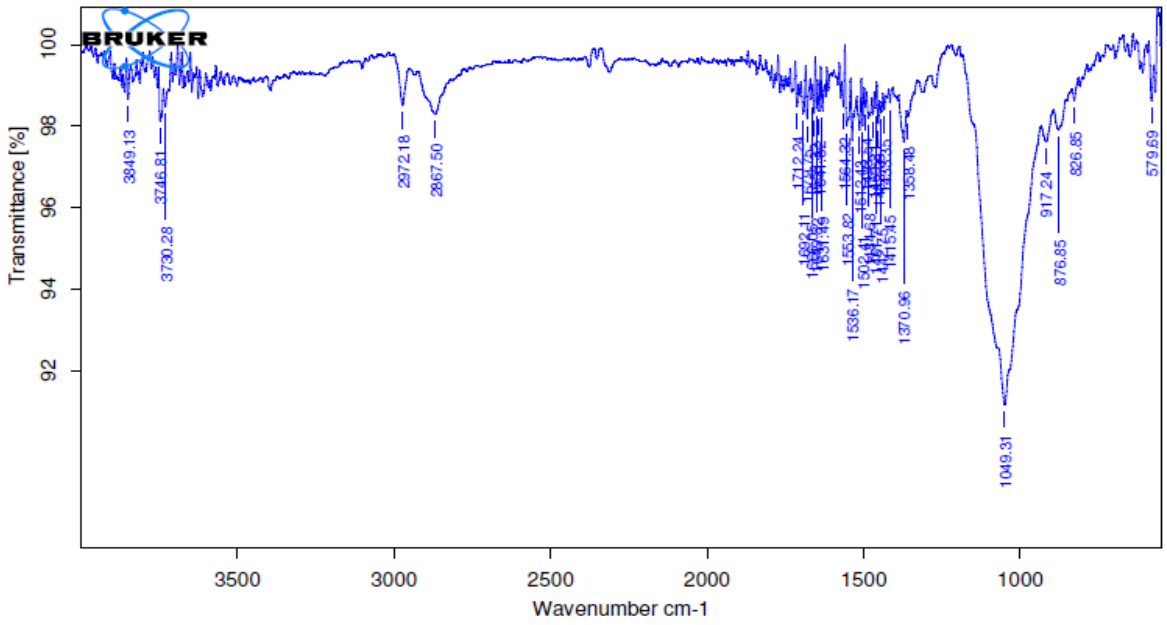

Fig-1: FTIR Studies of Granisetron

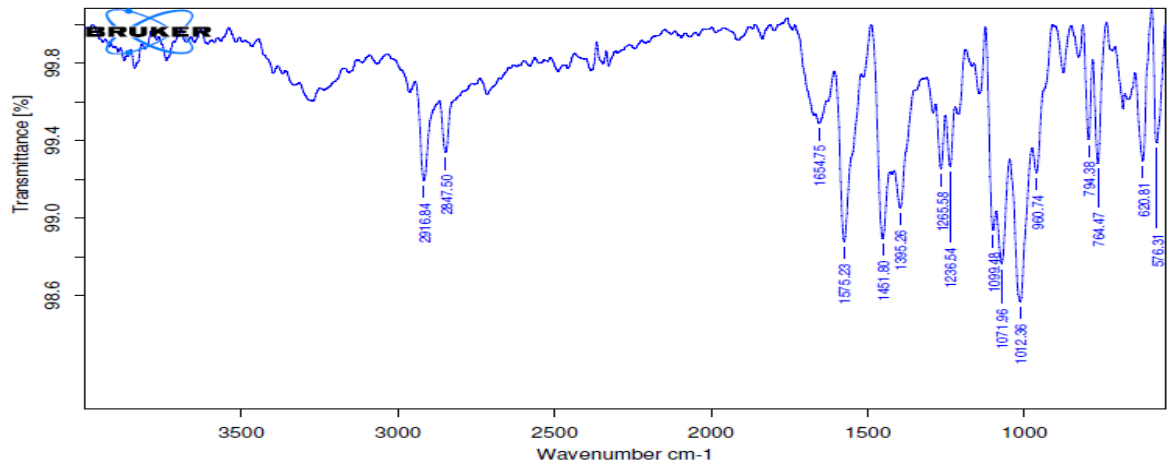

Fig-2: FTIR Studies of physical mixture of drug and excipients

EVALUATION STUDIES

Pre compression parameters

a) **Bulk Density:** The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.319-0.353.

b) **Tapped density:** The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.423-0.461.

c) **Angle of repose:** The angle of repose for the formulated blend was carried out. It concludes that all the formulations blend was found to be in the range of 28 to31^0

c) **Compressibility index:** Compressibility index was carried out, it found between 10% to 25.46 % indicating the powder blend have the required flow property for compression.

Characterization of Formulation

Table-2: Pre compression parameters of Granisetron fast dissolving tablets

F. NO	Bulk density	Tapped density	Compressibility index	Angle of repose(0)
F1	0.326	0.423	22.93	29^0c
F2	0.345	0.456	24.34	29^0c
F3	0.353	0.461	23.42	28^0c
F4	0.338	0.448	24.55	28^0c
F5	0.322	0.430	25.11	30^0c
F6	0.319	0.428	25.46	29^0c
F7	0.329	0.436	24.54	30^0c
F8	0.319	0.426	25.11	29^0c

Post compression parameters

Weight variation: All the formulated (F1 to F8) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness: Tablets mean thickness (n=3) were uniform in F1 to F8 formulations and were found to be in the range of 2.0 mm to 2.6 mm.

Hardness: The measured hardness of tablets of each batch ranged between 4.19 to 4.50kg/cm^2. This ensures good handling characteristics of all batches.

Friability: The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity: The percentage of drug content for F1 to F8 was found to be between 89.60 % and 98.58% of Granisetron, it complies with official specifications.

Disintegration Time: In the presented studies, three different types of in vitro methods of tablet disintegration were used: those where the only factor leading to the disintegration was water wicking into the matrix of the tablet, the tests with water agitation or stirring, and the methods where direct destructive forces were put on the tested tablet, such as grinding or pressing with additional weight. Therefore, disintegration tests showed great variability in the data measured with different methods. The shortest registered disintegration time was 49 s, while the longest greatly exceeded 53 sec.

Wetting Time: The weight of the tablet before keeping in Petri dish was noted (W_b) using Shimadzu digital balance. The wetted tablet from the Petri dish was taken and re weighed (W_a) using the same. The shortest registered wetting time was 123 sec, while the longest greatly exceeded 166 sec.

Water absorption ratio:

The ability to absorb a large amount of water when exposed to an aqueous environment. The absorption of water results in breaking of tablets and therefore faster disintegration. The water absorption ratio (F6) was 88%.

Table-3: Evaluation parameters of Granisetron fast dissolving tablets

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Disintegration time(sec)	Wetting time (sec)	Water absorption ratio(%)
F1	99±0.32	2.3±0.34	3.22±0.28	0.48±0.22	95.99±0.30	30±0.42	112±0.40	55±0.43
F2	98±0.28	2.4±0.30	3.19±0.40	0.51±0.26	96.81±0.34	32±0.40	132±0.35	63±0.38
F3	100±0.41	2.6±0.36	3.33±0.42	0.49±0.22	97.86±0.28	41±0.36	128±0.32	78±0.42
F4	97±0.30	2.4±0.34	3.45±0.46	0.50±0.20	96.25±0.27	35±0.38	125±0.28	82±0.40
F5	100±0.25	2.2±0.38	3.29±0.42	0.48±0.32	97.63±0.30	40±0.36	130±0.26	75±0.39
F6	100±0.22	2.3±0.26	3.48±0.38	0.49±0.31	98.95±0.34	43±0.43	134±0.28	88±0.35
F7	98±0.34	2.0±0.30	3.25±0.36	0.51±0.36	95.96±0.33	41±0.48	128±0.30	79±0.37
F8	100±0.30	2.1±0.28	3.29±0.34	0.53±0.40	94.38±0.40	46±0.43	122±0.36	86±0.33

Dissolution studies

All the eight formulation of Granisetron fast dissolving tablets were subjected to in vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for period of time.

Table-4: Dissolution studies of all formulations

Time	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
5	25.65±0.56	25.02±0.62	24.18±0.47	28.14±0.39	29.65±0.42	32.15±0.43	26.90±0.62	26.98±0.69
10	39.56±0.48	38.25±0.65	37.81±0.52	36.58±0.42	40.24±0.38	42.38±0.48	38.17±0.58	36.85±0.58
15	44.28±0.50	43.45±0.60	42.58±0.43	44.27±0.50	52.18±0.45	56.95±0.50	45.28±0.43	44.28±0.53
20	69.35±0.46	68.57±0.58	67.84±0.40	66.28±0.53	70.28±0.40	78.81±0.53	68.95±0.54	67.18±0.62
25	78.56±0.52	77.19±0.50	78.29±0.52	79.14±0.45	86.21±0.42	89.99±0.49	79.63±0.51	80.96±0.65
30	89.25±0.45	88.27±0.63	90.96±0.49	93.24±0.46	95.38±0.46	98.25±0.51	89.25±0.53	92.15±0.68

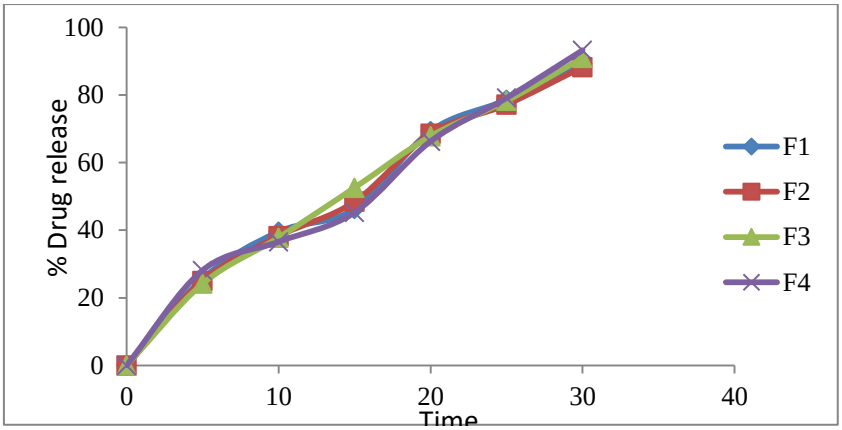

Table-3: Dissolution Profile of formulations (F1 to F4)

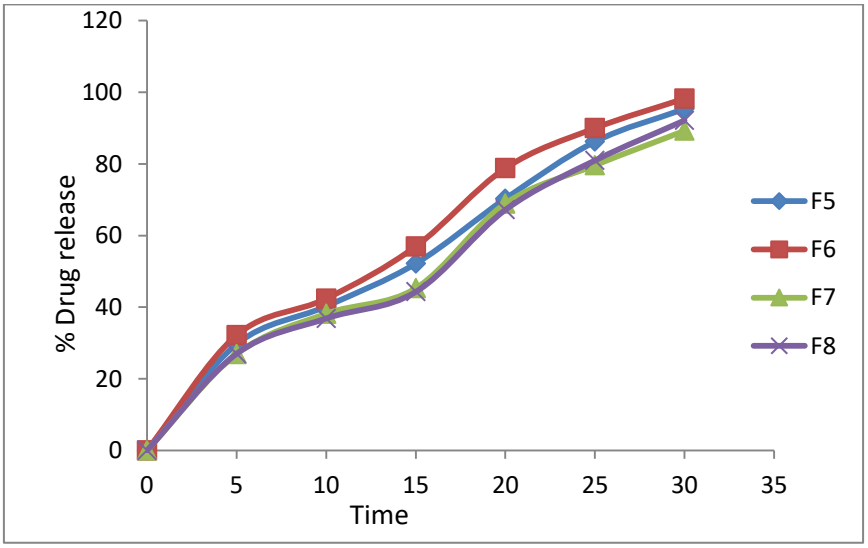

Table-4: Dissolution Profile of formulations (F5 to F8)

Kinetic modeling of drug release

All the eight formulation of prepared matrix tablets of Granisetron were subjected to in vitro release studies these studies were carried out using dissolution apparatus.

The results obtaining in vitro release studies were plotted in different model of data treatment as follows:

1. Cumulative percent drug released vs. time (zero order rate kinetics)
2. Log cumulative percent drug retained vs. time (First Order rate Kinetics)
3. Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
4. Log of cumulative % release Vs log time (Peppas Exponential Equation)

Table-5: Drug Release Kinetics of Formulation F6

TIME	%CDR	SQARE T	LOG T	Log % CDR	ARA	Log % ARA
0	0	0	0	0	0	0
5	32.15	2.236068	0.69897	1.507181	67.85	1.83155
10	42.38	3.162278	1	1.627161	57.62	1.760573
15	56.95	3.872983	1.176091	1.755494	43.05	1.633973
20	78.81	4.472136	1.30103	1.896581	21.19	1.326131
25	89.99	5	1.39794	1.954194	10.01	1.000434
30	98.25	5.477226	1.477121	1.992333	1.75	0.243038

Zero order kinetics

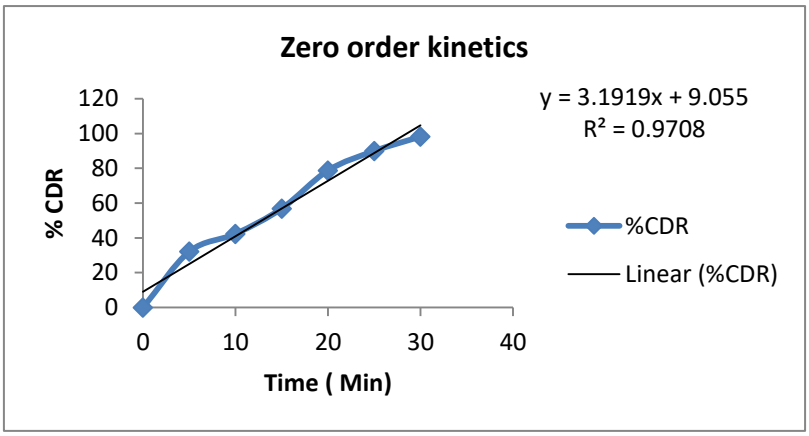

Fig-5: Zero order kinetics

First order kinetics

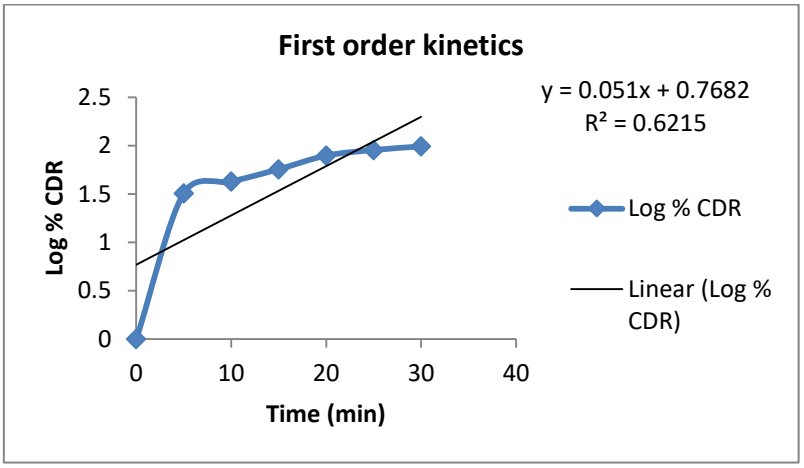

Fig-6: First order kinetics

Higuchi model

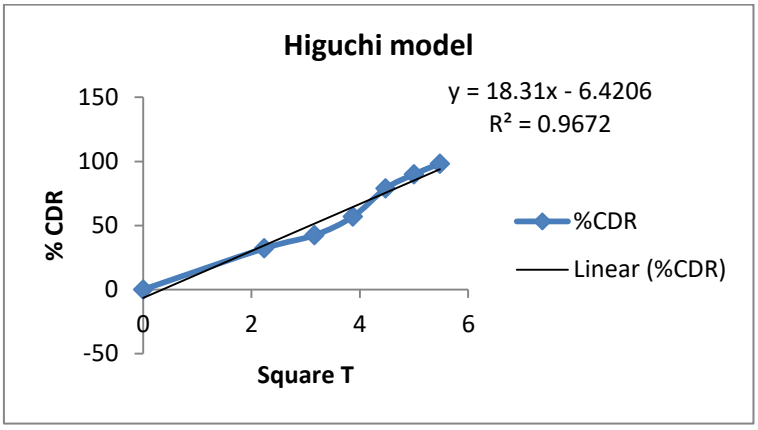

Fig-7: Higuchi model

korsmeyer peppas

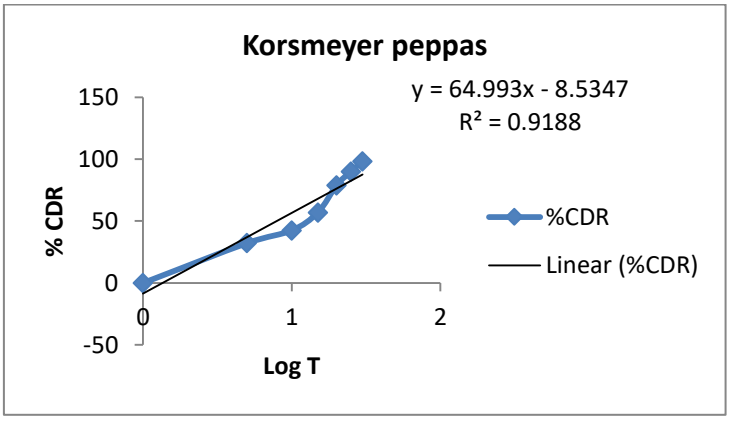

Fig-8: korsmeyer peppas

The kinetic values obtained for formulation F6 were shown. The values of in vitro release were attempted to fit into various mathematical models.

Regression values are higher with Zero order release kinetics. Therefore all the Granisetron tablets Zero order release kinetics. Therefore all the Granisetron fast tablets follow Zero order release kinetics.

Table-6: Regression equations of Granisetron tablets F6

Film code	In vitro release in phosphate buffer P^H 6.8 Regression values			
	Zero order	First order	Higuchi Plot	Korsmeyer peppas
F_6	0.970	0.749	0.967	0.918

The table indicates that r^2 values are higher for Higuchi's model compared for all the tablets. Hence Granisetron release from all the films followed diffusion rate controlled mechanism.

Stability Study

There was no significant change in physical and chemical properties of the tablets of formulation F-6 after 3 months. Parameters quantified at various time intervals were shown.

Table-7: Stability studies of all formulations

F. Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-6	**25^0C/60%RH % Release**	98.25±0.51	98.12±0.45	97.15±0.35	95.68±0.30	**Not less than 85 %**
F-6	**30^0C/75% RH % Release**	98.25±0.51	97.99±0.38	96.96±0.30	95.43±0.26	**Not less than 85 %**
F-6	**40^0C/75% RH % Release**	98.25±0.51	97.85±0.22	96.83±0.28	95.10±0.24	**Not less than 85 %**

4. CONCLUSION

It can be concluded that disintegration time and dissolution rate of granisetron can be enhanced to a great extent by direct compression technique with the addition of superdisintegrants. Further investigations are needed to confirm the *in-vitro* efficiency Fast dissolving tablets of granisetron were prepared using sodium starch glycolate, croscaramelose. Faster disintegration and significantly improved dissolution profile of granisetron from the proposed formulation could be highly beneficial for the prevention and treatment of patient population experiencing severe nausea and vomiting. From the FTIR study, it was confirmed that the drug and excipients in the formulations were compatible with each other. Hence the availability of various technologies and the manifold advantages of fast dissolving tablets will surely enhance the patient compliance providing rapid onset of action. The fast dissolving tablets of granisetron were successfully prepared using different superdisintegrants. Among all the superdisintegrants, sodium starch glycolate was found to be the best as it was effective even at least concentration level. The results of studies aid in the judicious selection of superdisintegrants and other adjuvants to formulate simple, convenient, cost effective and patient friendly dosage form. Overall results indicate that formulation F6, which contain sodium starch glycolate was a better one and satisfies all the criteria as fast dissolving tablet.

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