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FORMULATION AND EVALUATION OF ORAL DISINTEGRATING TABLETS OF GRANISETRON

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Abstract:

The objective of necessary work to develop Granisetron oral disintegrating tablets using different super disintegrants which would rapidly in oral cavity. Nine batches of Granisetron orally disintegrating tablets were prepared by direct compression method using sodium starch glycolate, crosscarmellose sodium, Crosspovidone as Superdisintegrants in different concentration in order to achieve faster disintegration of tablet. The influence of the Superdisintegrant concentration on the release of Granisetron was studied. The formulation batches were characterized by different physical parameters; physical parameters of all formulated tablets were within acceptable limits. The study reveals that the formulation Sodium starch Glycolate as disintegrant shows faster disintegration compare to others. The F3 formulation was released 96.98% and consider as a optimized.

Key words: *Orally disintegrating tablets, Sodium starch Glycolate, Granisetron, and Direct compression.*

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INTRODUCTION:

The oral route of administration is considered as the most widely accepted route because of its convenience of self administration, compactness and easy manufacturing. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients incompliance particularly in case of pediatric and geriatric patients. [1] but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water. [2] Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Orally disintegrating tablets are appreciated by a significant segment of populations particularly who have difficulty in swallowing. It has been reported that Dysphagia. [3] (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients ,psychiatric patients and patients with nausea, vomiting, and motion sickness complications. ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population.

This dosage form combines the advantages of dry and liquid formulation. Some novel ODT technology allow high drug loading, have an acceptable taste, offer a pleasant mouth felling, leaving minimal residue in the mouth after oral administration.ODT have been investigated for their potential in improving bioavaibility of poorly soluble drug through enhancing the dissolution profile of the drug and hepatic metabolism drugs. Orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets,porous tablets, and rapimelts. However, of all the above terms, United States pharmacopoeia (USP) approved these dosageforms as ODTs. Recently, European Pharmacopoeia has used the term orodispersible tablet for tablets that disperses readily and within 3 min in mouth before swallowing. [4]

United States Food and Drug Administration (FDA) defined ODT as “A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue.” The disintegration time for ODTs generally ranges from several seconds to about a minute. [5]

Drug selection criteria:

The ideal characteristics of a drug for oral dispersible tablet include

- Ability to permeate the oral mucosa.
- At least partially non-ionized at the oral cavity pH.
- Have the ability to diffuse and partition into the epithelium of the upper GIT.
- Small to moderate molecular weight.
- Low dose drugs preferably less than 50 mg.
- Short half life and frequent dosing drugs are unsuitable for ODT.
- Drug should have good stability in saliva and water.
- Very bitter or unacceptable taste and odor drugs are unsuitable for ODT[6]

Desired criteria for ODTs:

- ODT should leave minimal or no residue in mouth after oral administration, compatible with pleasing mouth feel.
- Effective taste masking technologies should be adopted for bitter taste drugs.
- Exhibit low sensitivity to environment condition such as humidity and temperature.
- ODTs should dissolve / disintegrate in the mouth in matter of seconds without water.
- Have sufficient mechanical strength and good package design.
- The drug and excipients property should not affect the orally disintegrating tablets.
- Be portable and without fragility concern.[7,8]

Advantages of ODTs:

The advantages of ODTs include :

No need of water to swallow the tablet.

- Compatible with taste masking and have a pleasing mouth feel.
- Can be easily administered to paediatric, elderly and mentally disabled patients.
- No residue in the oral cavity after administration.
- Manufacturing of the tablets can be done using conventional processing and packaging equipments at minimum cost. Allow high drug loading.
- Accurate dose can be given as compared to liquids.
- Dissolution and absorption of the drug is fast, offering a rapid onset of action.
- Advantageous over liquid medication in terms of administration as well as transportation. Some amount of drugs is absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach, thus reducing first pass metabolism, which offers improved

bioavailability and thus reduced dose and side effects.
- No risk of suffocation due to physical obstruction when swallowed, thus offering improved safety.
- ODTs are suitable for sustained and controlled release actives.
- Unit packaging. [9,10]

Approaches For Preparation Of ODTs:
Various preparation techniques have been developed on the basis of different principles, thus present different properties of ODTs by means of mechanical strength, stability, mouth feel, taste, swallowability, dissolution profile and bioavailability. Some of those technologies are patented. Basic pharmaceutical processes to manufacture ODTs are explained as follows:

Spray drying:
Spray drying methods are used to a great extent in pharmaceutical and biochemical procedures. Spray drying provides a rapid and economically efficient way to eliminate solvents and produces highly porous and fine powders. The formulations are compounded by hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, croscarmellose sodium or sodium starch glycolate as disintegrating agent. An acidic material (e.g., citric acid) or alkali material (e.g., sodium bicarbonate) is used to improve disintegration and dissolution behaviour. Tablets prepared by the compression of spray dried powder, when immersed in an aqueous medium, showed a disintegration time of 20 s. [15,16]

Sublimation:
Compressed tablet which contains highly water-soluble components can show slo dissolution behaviour, due to the low porosity of the tablets that reduces water penetration into the matrix. By conventional methods, volatile materials are compressed into tablets, these volatile materials can be removed by sublimation, which results in extremely porous structures. The volatile materials which can be used are ammonium carbonate, urea, ammonium bicarbonate, camphor and hexa methylene tetramine. In a few cases, thymol, menthol, camphor, an organic acid such as adipic acid and fatty acid such as arachidic acid, myristic acid, capric acid, and palmitic acid were used as the volatile materials and the sublimation temperature ranged from 40 ^{0}C to 60 ^{0}C. The disintegration time in the oral cavity was found to be about 25 s [17,18].

Freeze drying:
Lyophilization process involves removal of solvents from a frozen drug solution or a suspension containing structure-forming excipients. The tablets formed by this process are usually very light and have highly porous structures that allow, rapid dissolution or disintegration. Lyophilization is done at very low temperature to eliminate the adverse thermal effects that may alter drug stability during processing. The freeze dried dosage form have relatively few stability concerns during its shelf life. The drying process may give rise to the glassy amorphous structure of excipients and drug substance. [19,20]

Molding:
Molded tablets are made up of watersoluble ingredients. The powder mixture is sprinkled with a solvent (usually water or ethanol). The mixture is molded into tablets under pressure. Applied pressure should be lower than those used in conventional tablet compression. This process is also known as compression molding. Air drying can be used to remove the solvent. Due to lower pressure; a highly porous structure is created, that enhances the dissolution. The powder blend should be passed through a very fine screen, to improve the dissolution rate. Molded tablets disintegrate more rapidly and provide improved taste because of their highly water-soluble, sugar components. However, molded tablets generally do not have high mechanical strength. The chances of breakage of the molded tablets during tablet handling and opening of blister pockets, is very high. If the hardness enhancing agents are used in the formulation, decrease in disintegration rate is observed. Mechanical strength and good disintegration of the tablets can be improved by using non-conventional equipment and by using multistep processes [21,22].

Mass extrusion:
The mass extrusion technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol and methanol. Expulsion of softened mass through the extruder or syringe is carried out, to get a cylinder of the product which is then cut into even segments using a heated blade to form tablets.[23,24]

Direct compression:
Direct compression is the easiest and costeffective tablet manufacturing process. This method can be applied to manufacture ODT by selecting appropriate combinations of excipients, which can provide fast disintegration and optimum physical resistance. Sugar-based excipients are widely used as bulking

agents because of their aqueous solubility, sweetness pleasing mouth feel, and good taste masking. Tablets obtained by conventional compression method are less friable, but disintegrate more slowly. The compression method, with or without wet granulation, is a convenient and cost effective way to prepare tablets with sufficient structural integrity .[25,26]

Ideal characteristics of ODTs

ODTs should depict some ideal characteristics to distinguish them from traditional conventional dosage forms. Important desirable characteristics of these dosage forms include

1. No water requirement for swallowing purpose but it should dissolve or disintegrate in the mouth usually within fraction of seconds.
2. Provide pleasant feeling in the mouth.
3. Be compatible with taste masking.
4. Be portable without fragility concern.
5. Leave negligible or no residue in the mouth after oral administration.
6. Exhibit low sensitivity to altered environmental conditions such as humidity and temperature.
7. Allow high drug loading.
8. Adaptable and amenable to conventional processing and packaging equipment at nominal expense.

Mechanisms Of ODTs:

ODTs involve the following mechanisms to achieve the desired fast dissolving characteristics :

1. Water must quickly enter into the tablet matrix to cause rapid disintegration and instantaneous dissolution of the tablet.

2. Incorporation of an appropriate disintegrating agent or highly water soluble excipients in the tablet formulation.

3. There are some under mentioned mechanisms by which the tablet is broken down into the smaller particles and then subsequently result a solution or suspension of the drug. The mechanisms are-

- High swellability of disintegration
- Chemical reaction

Capillary action

MATERIALS:

Granisetron Procured From Dr. Reddy's laboratories. Provided by SURA LABS, Dilsukhnagar, Hyderabad. Sodium starch glycolate S.D. Fine Chem. Ltd., Mumbai, India Cross carmellose sodium S.D. Fine Chem. Ltd., Mumbai, India Cross povidone S.D. Fine Chem. Ltd., Mumbai, India .Aspartame S.D. Fine Chem. Ltd., Mumbai, India Talc S.D. Fine Chem. Ltd., Mumbai, India Magnesium StearateS.D. Fine Chem. Ltd., Mumbai, India Microcrystalline cellulose 102 S.D. Fine Chem. Ltd., Mumbai, India.

METHODOLOGY:

Buffer preparation:

Preparation of 0.2 M Potassium dihydrogen orthophosphate solution: Accurately weighed 27.128 gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000 ml of distilled water and mixed.

Preparation of 0.2 M sodium hydroxide solution: Accurately weighed 8 gm of sodium hydroxide pellets were dissolved in 1000 mL of distilled water and mixed.

Preparation of pH 6.8 phosphate buffer: Accurately measured 250 mL of v0.2 M potassium dihydrogen orthophosphate and 112.5 mL of 0.2 M NaOH was taken into the 1000 mL volumetric flask. Volume was made up to 1000 mL with distilled water.

Analytical method development for Granisetron:

a) Determination of absorption maxima

A spectrum of the working standards was obtained by scanning from 200-400 nm against the reagent blank to fix absorption maxima. The λmax was found to be 300nm. Hence all further investigations were carried out at the same wavelength.

b) Construction of standard graph

100 mg of Granisetron was dissolved in 100 mL of pH 6.8 phosphate buffer to give a concentration in 1mg/mL (1000µg/mL) 1 ml was taken and diluted to 100 ml with pH 6.8 phosphate buffer to give a concentration of 0.01 mg/ml (10µg/ml). From this stock solution aliquots of 0.5 ml, 1 ml, 1.5 ml, 2.0 ml, 2.5 ml, were pipette out in 10 ml volumetric flask and volume was made up to the mark with pH 6.8 phosphate buffer to produce concentration of 5,10,15,20 and 25µg/ml respectively. The absorbance of each concentration was measured at respective (λmax) i.e., 300 nm.

Table1: Formulation composition for tablets
Formulation table showing various compositions

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Granisetron	1	1	1	1	1	1	1	1	1
Sodiumstarch glycolate	10	20	30	-	-	-	-	-	-
Cross carmellose sodium	-	-	-	10	20	30	-	-	-
Cross povidone	-	-	-	-	-	-	10	20	30
Aspartame	5	5	5	5	5	5	5	5	5
Talc	3	3	3	3	3	3	3	3	3
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Microcrystalline cellulose 102	69	59	49	69	59	49	69	59	49
Total weight	100	100	100	100	100	100	100	100	100

All the quantities were in mg

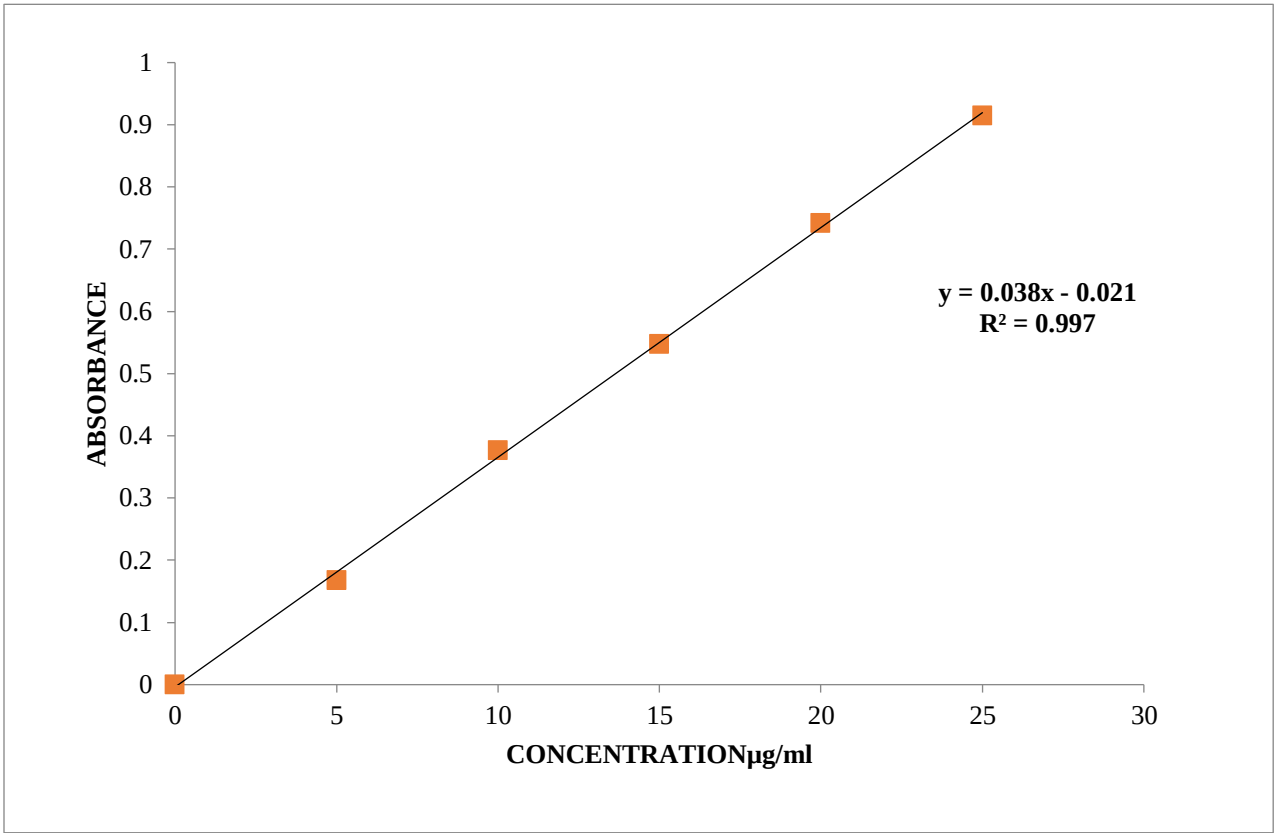
RESULTS AND DISCUSSION:

Preparation of calibration curve of Granisetron:

The regression coefficient was found to be 0.997 which indicates a linearity with an equation of y=0.038 x-0.021. Hence Beer-Lambert's law was obeyed.

Table2: Calibration curve data of Granisetron in pH 6.8 phosphate buffer

Concentration µg/ml	Absorbance at 300 nm
0	0
5	0.168
10	0.376
15	0.547
20	0.742
25	0.914



Preformulation parameters of powder blend

Table3: Evaluation of pre-compression parameters of powder blend

Formulation code	Angle of repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's ratio
F1	31.8 ± 0.08	0.30 ± 0.08	0.36 ± 0.15	16.6 ± 0.69	1.20 ± 0.22
F2	32.6±0.02	0.20 ± 0.57	0.25 ± 0.31	20.0 ± 0.12	1.25 ± 0.58
F3	30.1 ± 0.12	0.25 ± 0.05	0.31 ± 0.09	19.3 ± 0.78	1.24 ± 0.57
F4	31.3±0.04	0.21 ± 0.66	0.25 ± 0.51	16.0 ± 0.18	1.19 ± 0.63
F5	30.2 ± 0.08	0.21 ± 0.46	0.25 ± 0.2	16.0 ± 0.01	1.19 ± 0.63
F6	31.2±0.04	0.37 ± 0.18	0.45 ± 0.3	17.7 ± 0.74	1.21 ± 0.64
F7	31.6±0.09	0.25 ± 0.18	0.30 ± 0.44	16.6 ± 0.71	1.20 ± 0.26
F8	30.9±0.08	0.25 ± 0.75	0.30 ± 0.34	16.6 ± 0.51	1.21 ± 0.19
F9	32.5±0.04	0.33 ± 0.12	0.37 ± 0.11	10.8 ± 0.9	1.12 ± 0.81

All the values represent n=3

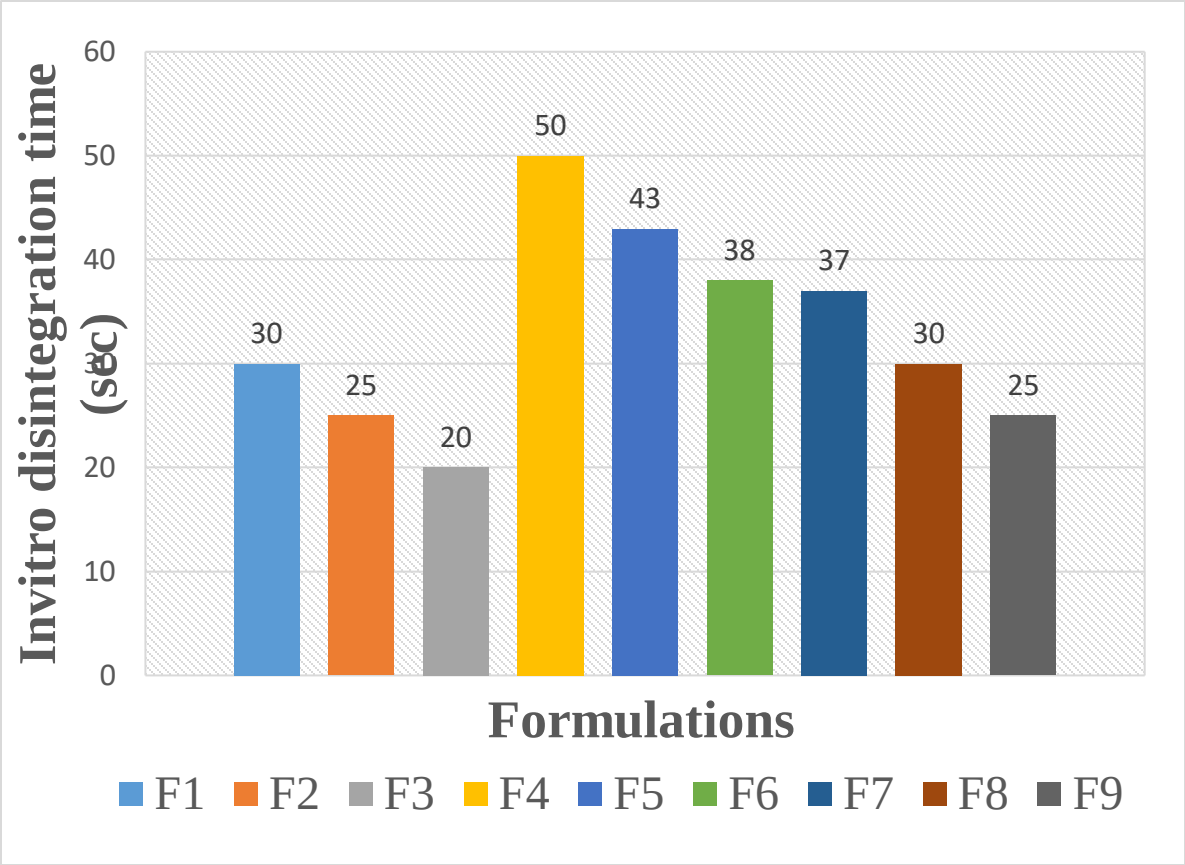
Quality control parameters for tablets:

Table:4 Evaluation of post compression parameters of Granisetron Fast dissolving tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	*In vitro* disintegration time (Sec)

F1	98.3±1.24	4.5 ±0.02	0.12	2.88 ±0.02	99±0.68	30
F2	97.4±0.24	4.5±0.10	0.27	2.84±0.03	99±0.88	25
F3	99.8±0.67	4.2±0.02	0.22	2.81±0.02	98±0.31	20
F4	96.5±0.47	4.5±0.01	0.18	2.89±0.03	97±0.57	50
F5	95.7±0.33	4.5±0.04	0.25	2.85±0.09	98±0.04	43
F6	99.3±0.82	4.4±0.00	0.19	2.88±0.06	99±0.28	38
F7	98.5±0.32	4.5±0.10	0.21	2.89±0.03	98±0.61	37
F8	97.8±0.61	4.5±0.06	0.26	2.83±0.03	97±0.53	30
F9	98.1±0.99	4.5±0.09	0.23	2.86±0.08	98±0.25	25

Disintegration Graph of F1-F9 Formulations:



***In Vitro* Drug Release Studies**

Table: *IN VITRO* DRUG RELEASE SYUDIES OF GRANISETRON

Table5: Dissolution data of Granisetron

TIME (MIN)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	55.76	58.22	63.54	48.32	51.43	62.96	45.36	50.95	56.76
10	68.93	72.31	74.19	57.23	62.19	71.75	55.89	61.55	64.82
15	71.32	80.24	82.37	72.33	76.67	81.45	71.36	73.34	77.11
20	82.17	85.67	88.25	79.51	85.46	86.31	76.28	82.18	84.67
30	91.62	94.39	96.98	88.77	92.73	93.89	85.76	87.24	89.35

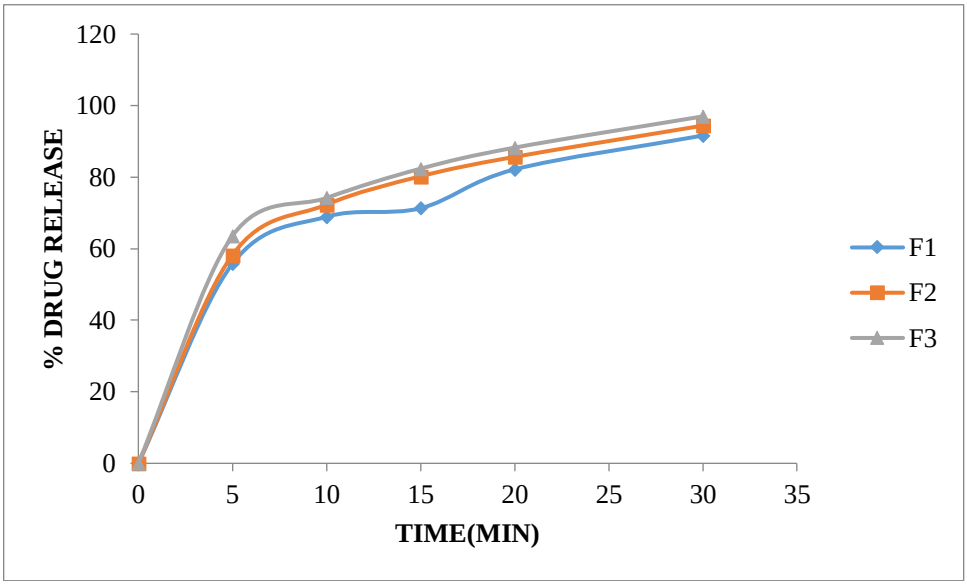


Fig1: Dissolution profile of formulations F1, F2, F3

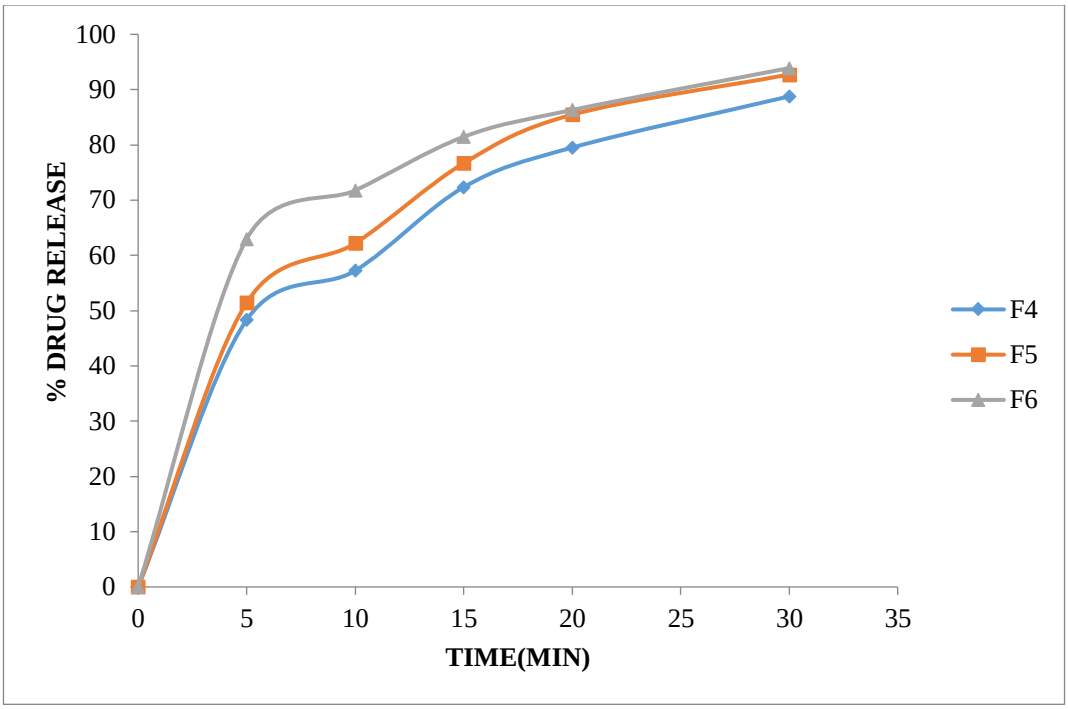


Fig2: Dissolution profile of formulations F4, F5, F6

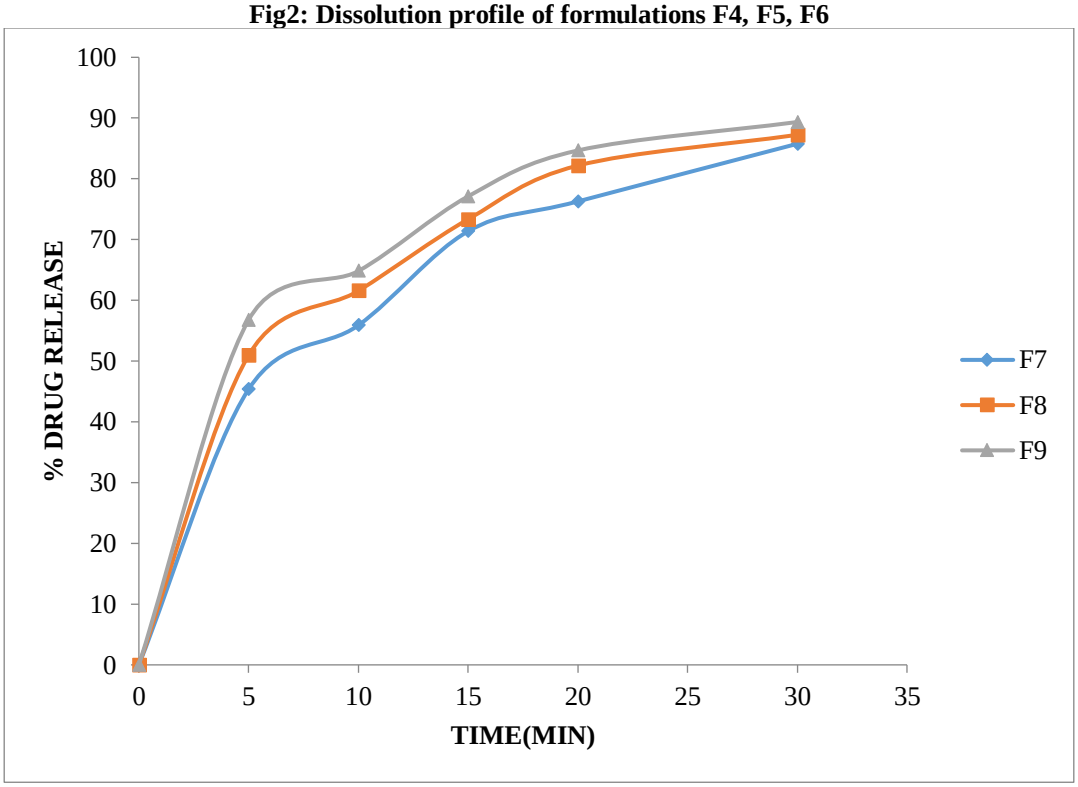


Fig5: Dissolution profile of formulations F7, F8, F9

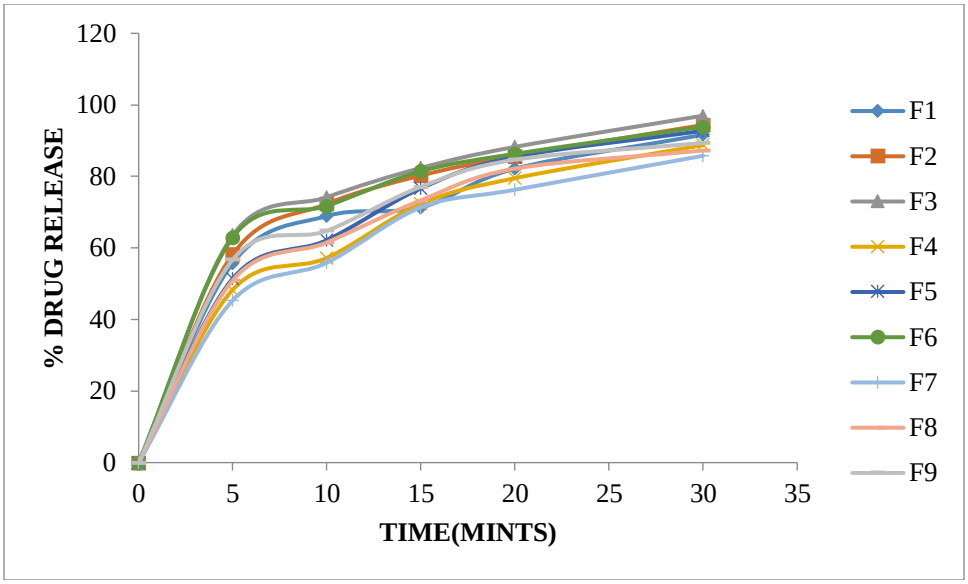


Fig 6: Dissolution profile of all formulations F1-F9

Drug – Excipient compatibility studies

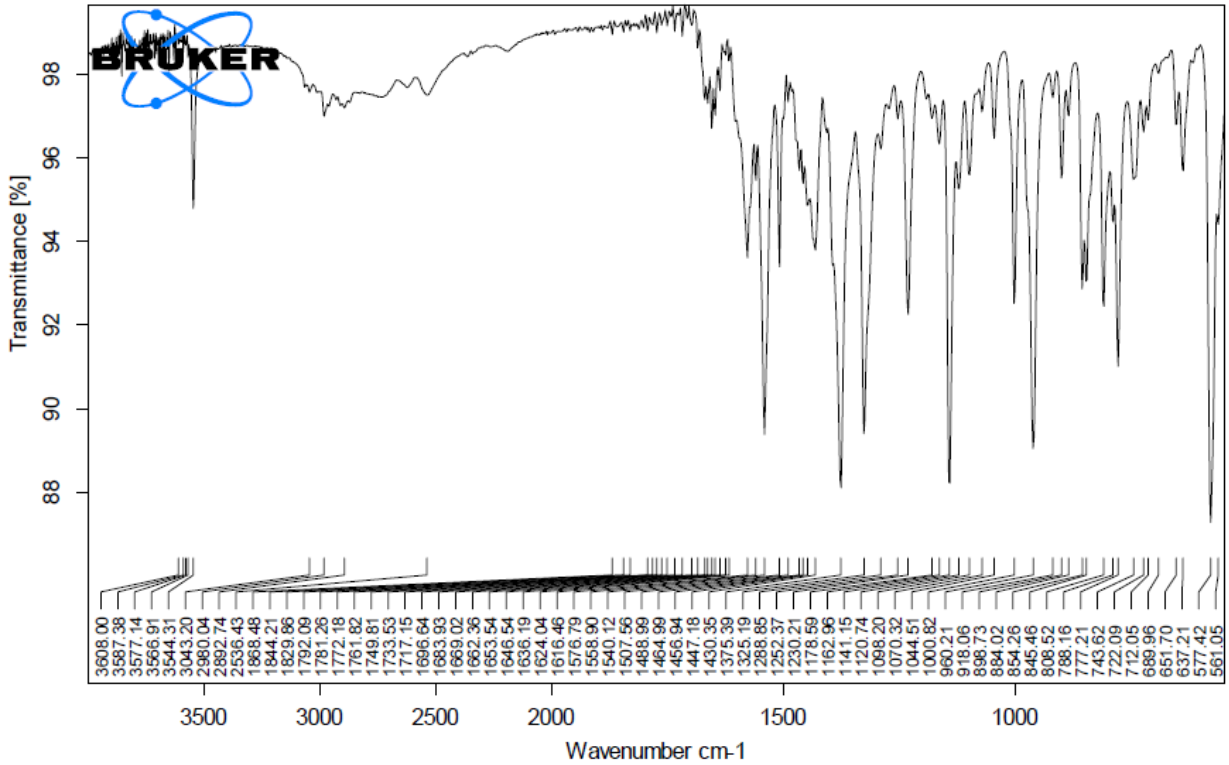


Fig 7: FTIR of Granisetron Pure Drug

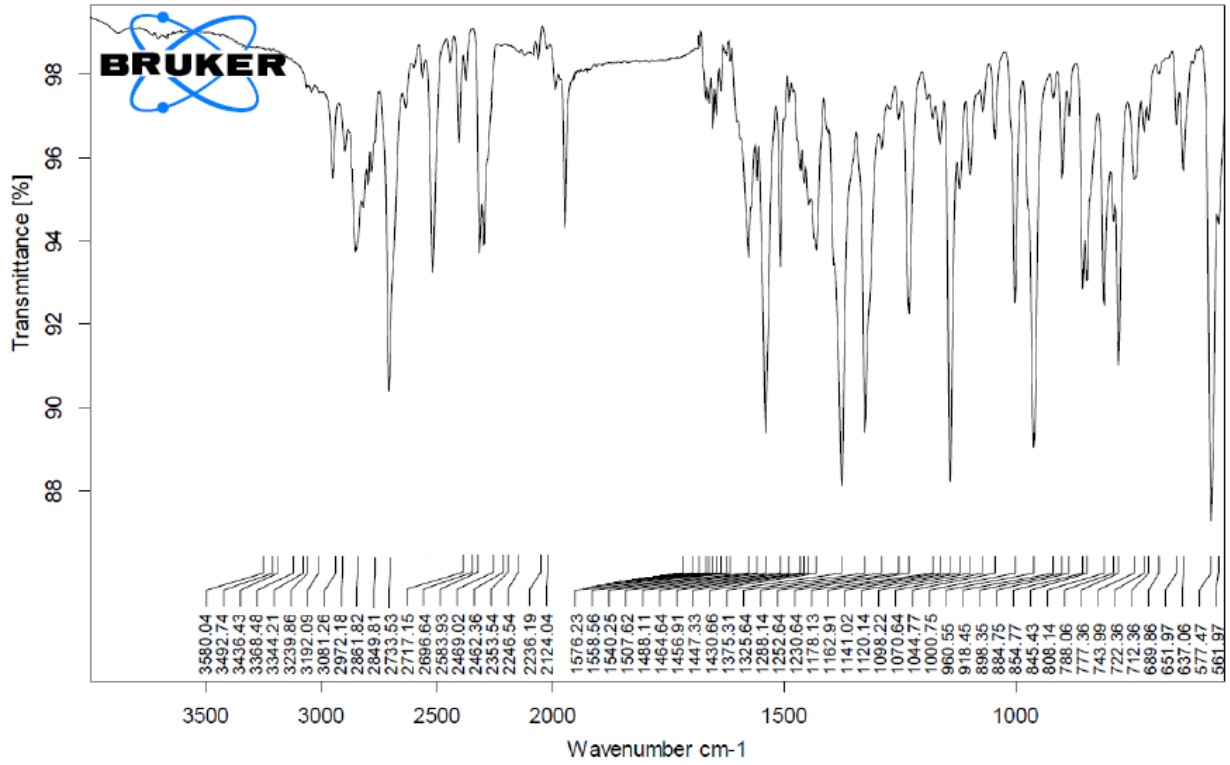


Fig8: FTIR of Granisetron optimized formulation

CONCLUSION:

Oral disintegrating tablets of Granisetron were developed by using different disintegrants to avert the problem of swallowing and provide rapid onset of action, which improves patient compliance and quality of life. The result of this study concluded that superdisintegrants addition technique was an interesting way of formulating oral disintegrating tablets using direct compression which is easy, inexpensive and does not require special production equipment. The pre-compression and post compression parameters are within limits. The F3 formulation was showed good drug release than the other formulations. The F3 formulation was released 96.98% and consider as an optimized.

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