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Formulation and evaluation of fast disintegrating tablets of ondansetron hydrochloride dihydrate using *Glycine max* (L.) Merr. Husk as superdisintegrant

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Abstract
The present scenario of pharmaceutical technology is changing continuously with every addition of new excipient for various solid dosage forms. Disintegrant is a common and most essential part of solid dosage forms such as tablet, capsules etc. It is an excipient in solid dosage form and has a major role to play. There are many substances act as disintegrant having advantages over each other. With the fast growing Pharma sector the number of such substances increasing day by day as per the need of industry. This makes the formulator to think over each and every aspect of the disintegrant for choosing it in his formula. Disintegrants are additives which cause a compressed tablet to break when placed in an aqueous media. Disintegrants are used to break (disintegrate) the intact tablet or capsule into smaller particulates so as to increase dissolution and increase faster action of dosage form. This alters the pharmacokinetics of dosage form.

Keywords: disintegrant, ondansetron, OND, husk, superdisintegrants, dispersion time

1. Introduction

Recently pharmaceutical preparations used for elderly patients have been investigated to improve the treatment compliances of patients (Ishikawa, 1999). Recent advances in novel drug delivery system aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is "Fast disintegrating Tablet" (Seager, 1998, Chang *et al*, 2000, Dobetti 2001, Kuchekar, Mahjan, 2004) [24, 5, 8, 19].

The concept of fast disintegrating drug delivery system emerged from the desire to provide patient with conventional mean of taking their medication. Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients (Lindgreen and Janzon, 1993) [20]. Other categories that experience problems using conventional oral dosage forms includes the mentally ill, uncooperative and nauseated patients, those with conditions of motion sickness, sudden episodes of allergic attack or coughing. These problems led to the development of novel type of solid oral dosage form called "Fast disintegrating Tablets". This tablet disintegrates instantaneously when placed on tongue, releasing the drug that dissolves or disperses in the saliva. On placing fast disintegrating tablet in the mouth, saliva serves to rapidly disintegrate the dosage form. The saliva containing the dissolved or dispersed medicament is then swallowed and the drug is absorbed in the normal way. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach and it may produce rapid onset of action (Wilson *et al.* 1987). In such cases bioavailability of drug is significantly greater than those observed from conventional tablet dosage form (Seager, 1998) [24].

Advantages of Fast disintegrating tablets (Bagul, 2006) [3]

1. Rapid onset of action and may improve bioavailability
2. Patients having difficulty in swallowing tablet can easily administered
3. Useful for pediatric, geriatric and psychiatric patients
4. Suitable during traveling or the situations where water may not be available
5. Improved patient compliance
6. Easy self administration (Honda, Nakano, 1998, Lindgreen, Janzon, 1993) [20, 12].

The mechanism by which tablet is broken down into smaller particles and then produces a homogeneous suspension or solution is based on:

i) Capillary action
ii) High swellability of disintegrants
iii) Capillary action and high swellability
iv) Chemical reaction (Adjei, Doyle, Reiland, 1992) [1].

Techniques for preparing fast disintegrating tablets

1) Direct compression (Ishikawa, 2001) [14]
2) Freeze drying (Corveleyn, Remon, 2000, Grother *et.al*, 1994.) [6, 11]
3) Tablet moulding (Dobetti, 2001.) [8]
4) Sublimation technology (Koizumi, 1997) [18]
5) Spray drying
6) Sugar based excipient (Davies, Allen, Wang, 2000) [7]
7) Acid-base effervescent technique (Ventura, Mezzadri, Brambilla, 2005.)

Methods of taste masking

1) Taste masking with sweeteners, flavors. (Fuisz, 1991, Reilly, 2002..) [9]
2) Taste masking by inclusion complexation.

3) Taste masking by ion-exchange resins (Agarwal, Mittal, Singh, 2000, Gao *et al*, 2003) [2, 10].

2. Materials and methods

2.1 Calibration Curve of Ondansetron (OND) (Patra, S. *et al*, 2007) [23]

Various drug concentrations (2-16 mcg/ml) in acidic buffer (pH 1.2) were prepared and the absorbance was noted at 310 nm. For the standard graph, 10mg of Ondansetron was dissolved in 100ml of acidic buffer (pH 1.2), 1ml of the solution were diluted to 100ml with acidic buffer (pH 1.2). Then 0.2ml, 0.4ml, upto 1.6 ml solution were withdrawn and diluted upto 10ml and absorbance was taken at 310 nm using UV spectrophotometer. The results are shown in Figure No.1.

2.2 Solubility study of Ondansetron in different media

Drug concentration 3, 6, 9, 12 mg/ml was kept in solubility medium such as pH 1.2, 4, 6.8, 7.2, 0.1N sodium hydroxide and methanol. Then vials were shaken at 37 ^{0}C for 24 hours in mechanical shaker. After 24 hours the medium was filtered using Whatman filter paper and analyzed by UV. Then percent solubility in specific medium was calculated (Figure No. 2).

2.3 Drug identification test and drug-polymer interaction

- **UV spectroscopy:** Solution of drug (4mcg/ml) was prepared in acid buffer (pH 1.2) then spectrum was taken on UV spectrophotometer (Figure No. 3)
- **Differential scanning Calorimetry:** The thermal behaviour of Ondansetron hydrochloride, *Glycine max* husk, physical mixture of OND and *Glycine max* husk were examined by DSC by using DSC 60 Shimadzu model to confirm complexation (Figure No. 4). Sample was loaded into an aluminium pan, hermetically sealed under nitrogen and run at scanning rate of 15^0c/min over a temperature range of 50^0 to 300^0 in a dynamic nitrogen atmosphere. An empty sealed aluminium pan was used as a reference.
- **Fourier transform infra-red spectroscopy:** The drug, husk were subjected to Fourier Transform Infra Red (FTIR) studies to check drug-excipient interaction using FTIR (Shimadzu 8400 s). The potassium bromide disk method was used for preparation of sample. The infra red spectra of Ondansetron, Ondansetron and aspartame co-precipitate, physical mixture of Ondansetron and *Glycine max* husk, Ondansetron tablet after three months stability study shown in Figure No. 5.

Table 1: Composition of tablets

Batch Code / Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
OND	4	4	4	4	4	4	4	4	4
MCC	76	86	96	74	84	74	84	74	82
Husk Powder above#60,	-	-	-	2	2	-	-	-	-
Husk Powder below#60	-	-	-	-	-	2	2	-	-
Husk Powder below#100	-	-	-	-	-	-	-	2	4
Aspartame	8	8	8	8	8	8	8	8	8
Strawberry flavour	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Menthol	1	1	1	1	1	1	1	1	1
Magnesium stearate	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Total weight	90	100	110	90	100	90	100	100	100

2.4 Preparation of tablets

Ondansetron hydrochloride, microcrystalline cellulose and sucralose or aspartame were mixed with disintegrant (modified husk powder 2 to 10% w/w) for 15 minutes in porcelain mortar then passed through sieve # 60. This blend was mixed with strawberry flavour (0.9%w/w) and menthol (1%w/w) for 5 minutes and finally mixed with magnesium stearate for 5 minutes. The composition of tablet is shown in Table 1. The powder blends were evaluated for pre compression parameters. Subsequently powder blends were directly compressed by using 7 mm round flat faced punch of rotary tablet machine (Karnavati, India). Compression force and the magnesium stearate level (0.1% w/w) were kept constant for all formulations.

2.5 Post compression evaluation (Yunixia, B. *et al*, 1999) [25]

2.5.1 Tablet thickness

Tablet thickness was measured by Vernier caliper.

2.5.2 Hardness

The hardness is expressed as Kg/ cm^2. The tablet crushing load, which is the force required to break a tablet into halves by compression. It was measured using a tablet hardness tester (Pfizer Hardness Tester).

2.5.3 Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of six inches with each revolution. Pre weighed sample of tablets were placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

2.5.4 Content uniformity
Thirty tablets were randomly selected. Out of thirty tablets ten tablets were crushed into fine powder and assayed individually. The tablet should be within 85 to 115%.

2.5.5 Weight variation
USP weight variation test is done by weighing 20 tablets individually; calculating the average weight and comparing the individual tablet weight to the average weight variation tolerance (Table 2).

Table 2: Weight variation tolerance

Average weight of Tablet (mg)	Maximum % deviation allowed
130mg or less	10%
130mg to 324mg	7.5%
More than 324mg	5%

2.5.6 *In vivo* disintegration time
Six healthy human volunteers, whose informed consent was first obtained, were selected for the study. Each volunteer randomly took one tablet from each formulation and kept on the tongue. Time taken for complete disintegration of the tablet on the tongue was noted. It was expressed in seconds. These volunteers were instructed not to swallow the disintegrated mass of the tablet. They were instructed to thoroughly gargle their mouth with distilled water after the completion of test. Three trials were performed at different time intervals.

2.5.7 Water absorption ratio
Tablet was weighed initially then wetting was done in distilled water with procedure for wetting time then reweighed tablet. Water absorption ratio was calculated by following formula:

$$Water\ absorption\ ratio = Final\ weight - Initial\ weight\ /\ Initial\ weight$$

2.5.8 Dispersion time
In vitro dispersion time was measured by dropping tablets in a measuring cylinder containing 6ml of pH 6.8 (simulated saliva fluid) Three tablets from each formulation were randomly selected and vitro dispersion time was performed.

2.5.9 Disintegration test (Bertoni, M.*et al*, 1995)
Randomly six tablets were selected from each batch for disintegration test. Disintegration test was performed without disc in distilled water using USP disintegration apparatus.

2.5.10 Wetting time
The double folded absorbent paper was kept in a petridish and thoroughly wetted with phosphate buffer pH 6.8. The excess buffer was drained out of the petridish. Then tablet was placed at the centre of the wet paper. The time required for the buffer to diffuse from the absorbent paper throughout entire tablet was recorded using a stopwatch. This test was performed in triplicate and mean ± SD calculated (n = 3).

2.5.11 Stability studies of tablets
Tablets were stored at 40 ± 1^0C and 75% relative humidity in stability chamber (Remi Lab, Bombay). Samples were withdrawn at 1 month interval and evaluated for physical parameters.

3. Results and Discussion
3.1 Analysis of Ond
3.1.1 Calibration curve of OND in acidic buffer (pH 1.2)
The calibration curve for OND in acidic buffer (pH 1.2) was found to be in the concentration range of 2-16 mcg/ml and followed the Beer Lambert law

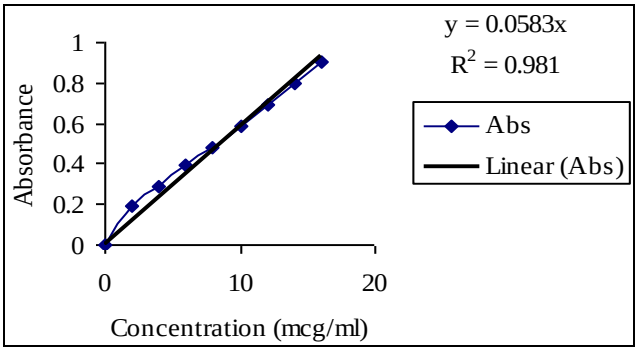

Fig 1: Calibration curve of OND in acidic buffer (pH 1.2)

3.1.2 Solubility study of OND in different media:
Percent solubility of OND in different media was found pH dependent. It decreases from acidic to basic pH. Solubility is highest in methanol (Figure No. 2).

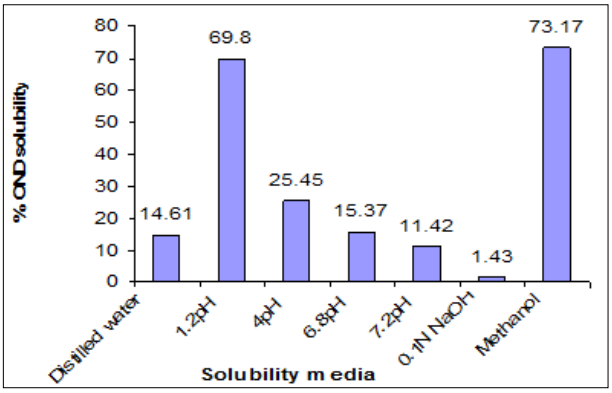

Fig 2: Percent solubility of OND in different media

3.1.3 Drug Identification and Drug-Excipient Interaction Study Uv Spectrum of Ond

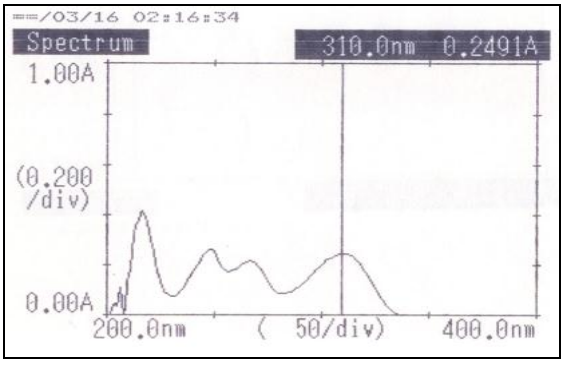

Fig 3: UV spectrum of OND in acid buffer (pH 1.2)

The UV spectrum of sample OND in acid buffer (pH1.2) shows four prominent peaks at wavelength 210nm, 249nm, 266nm, 310nm. These peaks are similar to the standard peaks, so confirmed identity of sample drug as OND.

Differential scanning calorimetry

DSC revealed information on solid-state interactions between OND and *Glycine max* husk. The DSC thermograms of pure components are in Figure No. 4. The DSC curve of OND has two sharp endothermic peaks out of those first at 107.36ºC indicated dehydration and second at 180.90ºC indicated melting point which were similar to peaks reported in literature. Characteristic peaks of OND were well recognized in the physical mixture of drug with husk. Thus there was no interaction between OND and *Glycine max* husk. After co precipitation drug was not hydrolyzed.

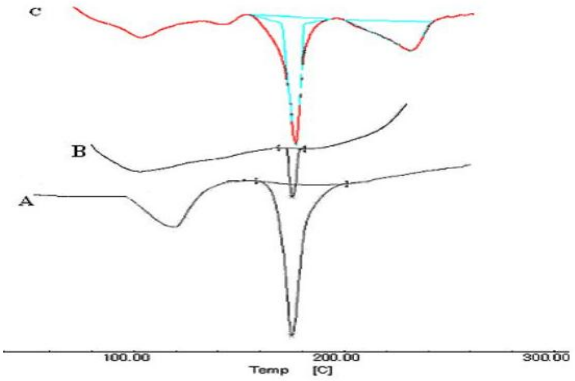

Fig 4: DSC Thermograms

A- DSC Thermogram of OND,
B- DSC Thermogram of OND: *Glycine max* husk physical mixture,
C- DSC Thermogram of OND: Aspartame coprecipitate

Fourier transformer infra red spectroscopy

Identification of OND was done by IR spectrum. There was no interaction found between OND and excipients. All peaks of IR spectrum of OND were remained unchanged.

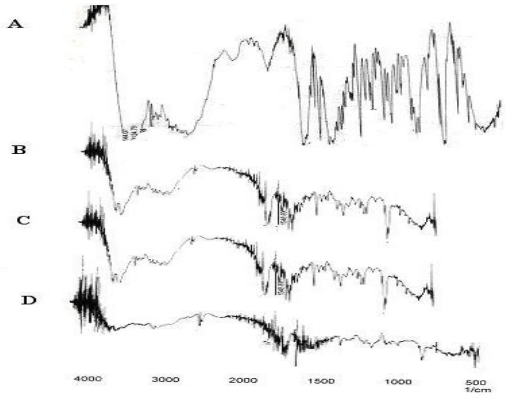

Fig 5: Infrared Spectra

A-Infrared Spectra of OND,
B- Infrared Spectra of OND: Aspartame co-precipitate,
C- Functional groups in OND: *Glycine max* husk physical mixture,
D- Infrared Spectra of OND tablet after 3 months stability study

3.2 Evaluation of formulation blends

Table 3: Physical characterization of formulation blends

Batch code / Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Angle of Repose (^{0})	22.45 ±0.18	23.55 ±0.25	23.25 ±0.29	25.03 ±0.19	26.52 ±0.22	25.45 ±0.24	25.33 ±0.30	24.21 ±0.19	25.21 ±0.28
Bulk density (mg/ml)	0.49	0.46	0.58	0.49	0.46	0.58	0.49	0.46	0.58
Tap Density (mg/ml)	0.52	0.58	0.74	0.52	0.58	0.71	0.54	0.58	0.72
Carr's Index (%)	5.76	20.68	21.62	5.769	20.68	18.30	9.25	20.68	19.44
Hausner's ratio	1.06	1.26	1.27	1.061	1.26	1.22	1.10	1.26	1.24
Dispersibility Dispersibility (%)	0.12 ±0.85	0.13 ±0.84	0.13 ±0.90	0.15 ±0.9	0.15 ±0.7	0.17 ±0.74	0.17 ±0.80	0.26 ±0.76	1.26 ±0.86

All values are mean ± SD, (n = 3)

Formulation F1, 2, 3 contains MCC as disintegrant as well as filler. Increased amount of MCC decreased porosity of tablet blend hence decreased compressibility (Jain, Goswami, 2005) [15] and flow property remained good (Martin, 1993) [21]. F4, 5 contains powder above # 60 and F6, 7 contains powder below # 60 as superdisintegrant and flow property, compressibility found to be good. F8, 9 contains powder below #100 have good powder characteristics and compressibility but higher dispersibility than F4, 5, 6, 7. It might be due to presence of smaller, light weight particles, as shown in Table No.3.

3.3 Evaluation of tablets

Table 4: Evaluation of formulated tablets

Batch code / Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight variation (mg)	89.35 ±4.098	99.21 ±4.716	100.14 ±4.25	89.36 ±2.52	99.25 ±3.12	89.36 ±1.52	99.25 ±3.24	99.56 ±1.96	99.81 ±3.52
Drug content (%)	89.45 ±0.08	99.21 ±0.76	100.14 ±0.2	89.36 ±0.5	99.25 ±0.2	89.36 ±0.2	99.25 ±0.2	99.56 ±0.9	99.81 ±0.2
Friability (%)	0.256 ±1.08	0.23 ±1.2	0.155 ±1.76	1.23 ±1.2	1.25 ±1.5	1.56 ±0.2	1.64 ±0.21	0.148 ±0.5	0.157 ±0.9
Hardness (Kg/cm^2)	12 ±1.94	13 ±4.25	14 ±3.24	5 ±3.12	6 ±2.12	6 ±2.2	7.2 ±3.5	8.4 ±3.2	7.6 ±3.1
Thickness (mm)	3 ±0.2	3 ±0.56	3.2 ±0.5	3 ±0.36	3 ±0.32	3 ±0.02	3 ±0.62	3 ±013	3 ±0.23
Disintegration time *in vitro* (sec)	193 ±3.2	196 ±3.2	201 ±4.2	20.66 ±2.5	26.15 ±1.2	22.17 ±3.2	28.13 ±4.76	30.66 ±3.2	36.15 ±5.08
Disintegration time i*n vivo* (sec)	25.12 ±5.0	26.17 ±4.70	28.13 ±3.5	15.26 ±2.5	13.24 ±3.2	11.23 ±1.9	19.21 ±4.2	23.14 ±1.2	26.25 ±1.9
Dispersion time (sec)	52.13 ±5.08	53.23 ±4.4	55.42 ±4.2	37.5 ±2.5	43.2 ±3.2	39.23 ±3.2	45.20 ±1.2	47.52 ±1	53.23 ±1.6
Wetting time (sec)	37.94 ±5.0	38.4 ±3.2	42.43 ±4.76	26.02 ±4.2	7.90 ±2.5	8.41 ±3.2	12.42 ±1.2	26.12 ±3.2	25.36 ±1.9
Water absorption ratio	1.22 ±5.4	1.23 ±3.2	1.26 ±1.2	1.28 ±3.2	1.214 ±1.9	1.43 ±4.76	1. 24 ±4.2	1. 82 ±2.5	1.32 ±3.2

All values are mean ± SD, (n = 3).

Formulation F1, 2, 3 physical parameters followed the standard limits but DT observed was more than 3 minutes which did not pass the criterion for fast disintegrating tablet. F4, 5 contains powder above # 60 and F6, 7 contains powder below # 60 as superdisintegrant and showed DT less than 30 seconds but leads to fail friability. F8, 9 contains powder below #100 have tablet properties remained inside the limits including friability. It was because of sufficient concentration of husk powder to produce compact tablet (Table No.4).

3.4 Stability Study of Optimized Fast Disintegrating Tablet

The results indicate that there wasn't any significant change in the taste and colour. All other tablet parameters remained within limits and no significant effect of storage conditions on tablet was observed (Table No. 5).

Table 5: Evaluation of OND tablets containing aspartame after one month stability.

Batch code / Parameter	F5	F6	F7	F8	F9
Weight variation (mg)	99.56 ±1.96	99.81 ±3.52	89.45 ±5.08	99.21 ±4.76	100.14 ±4.2
Drug content (%)	99.56 ±0.9	99.81 ±0.2	89.35 ±0.98	99.21 ±0.71	100.14 ±0.25
Friability (%)	0.148 ±0.5	0.157 ±0.9	0.149 ±0.15	0.156 ±0.11	0.35 ±0.25
Hardness (Kg/cm^2)	8.4 ±3.2	7.6 ±3.1	8.2 ±4.70	8.4 ±3.5	7.2 ±2.5
Thickness (mm)	3 ±013	3 ±0.23	3 ±0.2	3 ±0.56	3.2 ±0.5
Disintegration time *in vitro* (sec)	30.66 ±3.2	36.15 ±5.08	34.12 ±5.4	32.17 ±2.5	38.13 ±3.2
Disintegration time *in vivo* (sec)	23.14 ±1.2	26.25 ±1.9	14.56 ±5.0	16.56 ±3.2	15.88 ±4.2
Dispersion time (sec)	47.52 ±1	53.23 ±1.6	31.24 ±7.9	36.32 ±5.0	32.24 ±1.9
Wetting time (sec)	26.12 ±3.2	25.36 ±1.9	9.94 ±3.7	10.4 ±1.9	13.43 ±1.6
Water absorption ratio	1. 82 ±2.5	1.32 ±3.2	1. 32 ±0.2	1.13 ±0.5	1.16 ±0.34
Complete drug release (min)	8	8	7	7	5

All values are mean ± SD, (n = 3).

4. Summary and Conclusion

Particle size reduction of *Glycine max* husk changes physical properties to significant extent. Lesser the particle size more the cohesion and least dispersibility so less will be the weight loss during tablet manufacturing process. Powder below # 100 is optimum as superdisintegrant for tablet manufacturing and optimum concentration range is 2 to 10% by weight. OND taste masking is possible with aspartame and sucralose. F8 and F9 were best formulations in all aspects of fast disintegrating tablet. *Glycine max* husk can be used without any processing in tablets for its super disintegrating action. The dominant disintegrating mechanism is swelling of husk. *Glycine max* husk is chemically inert polymer as it did not show interaction with drug or other excipients in tablets even after accelerated stability study for one month.

This work concludes that *Glycine max* husk can be used as superdisintegrant for the fast disintegrating tablets. *Glycine max* husk will prove as potential, cheaper and stable excipient for tablet formulations.

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