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Formulation Development and Evaluation of Ondansetron Hcl Fast Dispersing Tablets for Treatment of Chemotherapy

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Abstract: ***The objective of the present investigation is to prepare fast dispersing tablets of ondansetron hydrochloride, because of its application in emesis condition, fast onset of action and avoidance of water is highly desirable. Tablets are prepared by direct compression of sodium starch glycolate, croscarmellose sodium and combination of both are used as superdisintegrants. Microcrystalline cellulose is used as binder and mannitol used as dilluent and sodium saccharin used as sweetening agent and magnesium stearate used as lubricant. All these ingredients are mixed together and compressed into tablets. Before punching into tablets the powder is evaluated for bulk density, tapped density, angle of repose and Carr's index. After punching the tablets are evaluated for weight variation, hardness, friability, in vitro disintegration time, wetting time, and drug release characteristics. Hardness and friability data indicated good mechanical strength of tablets. The results of in vitro disintegration time indicated that the tablets dispersed rapidly in mouth within one minute. It was also observed that the ondansetron hydrochloride prepared tablets drug releasing rate is faster than the pure drug. It is also concluded the order of drug releasing rate was found to be faster in case of tablets prepared by combination of super disintegrates < sodium starch glycolate < croscarmellose sodium.***

Keywords: Direct Tablet Compression, Fast Dispersing tablets, Ondansetron Hydrochloride, Friability, Hardness, Absorption of drug.

1. Introduction

The concept of fast dispersion or mouth dissolving drug delivery system emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and hard gelatin capsules. Hence, they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy.

In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Such problems can be resolved by means of mouth dissolving tablets when put on tongue these tablets disintegrate and dissolve rapidly in saliva without need of drinking water. The faster the drug disintegrates in to solution, the quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as saliva passes down into the stomach.

In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. Hence, in the present study an attempt will be made to formulate mouth Dissolving tablets of ondansetron (a selective serotonin 5-HT3 receptor antagonist) used as an anti nauseate and antiemetic agent indicated for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy and for the prevention of post operative nausea and vomiting.

Development of novel sustained-release (controlled-release) dosage forms offering a consistent plasma drug concentration throughout a specific period of time. These can then be accumulated and taken all at once for an enhanced drug effect, which can be very dangerous. A dosage form that does not remain intact once placed in the oral cavity would be useful when treating these patients. The liquid dosage forms often prescribed are easy to administer in comparison with tablets but suffers from the disadvantages of stability, packaging, inaccurate dosing and cost. Higher standards of living have increased the demand for dosage forms that are easily handled and readily available and can be taken anywhere. Patients appreciate the discreetness of the product, which can be taken without water and guarantees a rapid onset of action.

An immediate release drug delivery system (IRDDS) is the most convenient mode of administering drugs to overcome problems relating to swallowing difficulties. An immediate release (IR) system is a solid-tablet dosage form that dissolves or disaggregates spontaneously in the oral cavity, resulting in a solution or suspension without the need for the administration of water. Effectively it is a solid-dosage form providing the convenience of a liquid-dosage form [1-3]. The active pharmaceutical ingredient (API) dissolves instantly in the saliva, leading to comparatively fast absorption of the drug. These are also known as fast-dispersing, mouth dissolving, orally disintegrating, fast-melting, rapid-dissolve, rapid-melt or oro-dispersible tablets.

An ideal fast dispersion tablet (FDT) should combine the features of conventional tablets (hardness, friability, stability, and content uniformity) with additional parameters of porosity to rapidly absorb water and extreme ease of administration. The presence of features such as pleasant mouth-feel, minimal or no residue after oral administration, and cost-effectiveness would offer additional advantages However, all the desired parameters are often not achieved, especially the combination of hardness and strength with porosity, due to technological limitations.

The FDT should disperse/disintegrate in less than three minutes. The basic approach in development of FDT is the

use of superdisintegrants, like cross linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate (primogel, explotab), polyvinylpyrollidone (polyplasdone) etc, which provide instantaneous dispersion of tablet after putting on tongue, their by release the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. More ever, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablet.

2. Technologies for Preparing Fast Dispersing Tablets

The technologies used for manufacturing fast dispersing tablets are freeze-drying, spray-drying, tablet molding, sublimation, sugar-based excipients, direct tablet compression, and disintegration addition. As a result of increased life expectancy, the elderly constitute a large portion of the worldwide population today. These people eventually will experience deterioration of their physiological and physical abilities.

2.1 Direct Tablet Compression

Direct tablet compression is the simplest and least expensive tableting process. It uses conventional blending and tableting equipment as well as commonly available excipients. FDTs made by direct compression are robust and can be easily packaged and handled. However, in vivo disintegration time is longer (30-60 seconds) and good taste and mouth feel are harder to achieve. For unpleasant tasting drugs, current direct compression methods require a separate taste-coating process for the active ingredient prior to introduction into the direct compression process.

Separate processes used for taste-masking include wet granulation, roller compaction, spray-drying, and coating. Taste-coating may be based upon time or pH dependent dissolution of the coating polymer. Other taste-masking methods include the use of cyclodextrins, encapsulation using, electrochemical coating, and the use of supercritical fluids.

For direct compression fast dispersion tablet processes, sugar based excipients (mannitol, sorbitol, xylitol, maltose, etc.) are routinely used for their high water solubility, sweet taste, and pleasant mouth feel. In addition to taste and mouth feel, disintegration time is a primary concern. Some FDT technologies use effervescent couples alone or in combination with other disintegrants to achieve rapid dispersion [4-5]. The use of disintegrants, and especially the more modern superdisintegrants, has made the advent of compression based FDTs possible.

Various materials have been utilized as disintegrants. Starches and modified starches have a long history of use as disintegrants. Within this group, the superdisintegrant Sodium Starch Glycolate is of most interest today. This material is commonly used in levels of 2-8% by weight and its primary mechanism of action as a disintegrant is via swelling.

Crospovidone, cross-linked polyvinylpyrrolidone, is another superdisintegrant of choice. Although historically used in a range of 2-5%, one manufacturer recommends up to 15% by weight in FDT formulations. In fact, a specific grade featuring a smaller and narrower particle size distribution has been developed specifically to yield better mouth feel in FDT formulations. Crospovidone is said to promote both wicking and swelling. Crospovidone's disintegrant action is dependent upon compression force. Certain tablet hardness is required for the swelling and expansion to be effective. Modified celluloses are another common group of disintegrants. Most recommended among this group is Croscarmellose Sodium, an internally cross-linked Sodium Carboxymethycellulose. Typical use levels range from 2-4% although lower and higher amounts have been utilized.the dispersion works via both wicking and swelling.

Calcium Silicate in amounts up to 30% by weight has also been used to promote dispersion. RxCipie® FM 1000® Calcium Silicate from Huber Engineered Materials (Havre de Grace, Maryland) is extremely hydrophobic. When combined with superdisintegrants, the superdisintegrants are said to expand against this hydrophobic material. This expansion against another material is said to promote the tablet rapidly breaking down into primary particles. Other disintegrants employed in FDTs are Alginic Acid, Sodium Alginate, Microcrystalline Cellulose, Methacrylic Acid-Divinylbenzene Copolymer Salts, and Poly(Acrylic Acid) Superporous Hydrogel (SPH).

Inorganic excipients have also been utilized in direct compression FDTs. Dispersion is aided by the combination of disintegrant, insoluble materials, and soluble materials in specific ratios. Di-basic and Tri-basic Calcium Phosphate have been utilized as an insoluble inorganic material. Other insoluble excipients commonly used in tablets may contribute to the total amount of insoluble material used.

Lubrication is another important concern when making FDTs. Historically, Magnesium Stearate has been the most effective and most commonly used lubricant used in tableting processes to prevent tablets from sticking to the punch faces and to reduce friction between the die wall and the tablet during compression and ejection. It is commonly used in amounts of less than 2% with 1% or less being the preferred amount. Increases in the amount of Magnesium Stearate or the Magnesium Stearate mixing time tend to retard dispersion and dissolution and increase friability. In fact, some sources recommend against the use of Magnesium Stearate in FDTs because of its hydrophobic nature and tendency to increase disintegration time [6-7]. Sodium Stearyl Fumarate, a less hydrophobic material not sensitive to blending time, is generally recommended for use in FDTs. One method of producing FDTs is to use a method of lubricating the tablet and press external to the tablet formulation. One patent recommended levels of Magnesium Stearate up to 2.5% be used as a tablet lubricant in FDTs [9].

Table 1: Raw materials for preparation ondansetron hydro chloride

Ondansetron hydrochloride	Pure drug
Sodium starch glycolate	Superdisintegrants
Croscarmellose sodium	Superdisintegrants
Microcrystalline cellulose	Binder or excipient
Mannitol	Dilluent
Sodium saccharine	Sweetening agent
Magnesium state	Lubricant

3. Formulation of Tablets

All integrants are passed through 100 # screen. After this three groups are prepared, each group contains four batches.

3.1 Group A

For preparing 400 mg tablet, first mannitol and microcrystalline cellulose are weighed, incorporated in motor and pistor titrate in clock wise direction.

Table 2: Formulation of group A

Name	*F1 (mg)*	*F2 (mg)*	*F3(mg)*	*F4(mg)*
Ondansetron hydrochloride	8	8	8	8
Sodium starch glycolate	_	10	20	30
Croscarmellose sodium	_	_	_	_
Microcrystalline cellulose	330	320	310	300
Mannitol	50	50	50	50
Sodium saccharine	5	5	5	5
Magnesium state	4	4	4	4

3.2 Group B

In this group instead of sodium starch glycolate we are using croscarmellose as superdisintegrants. At first mannitol and microcrystalline cellulose are weighed accurately and incorporated in motor and pistor, then titrate in clock wise direction. Then sodium saccharine and croscarmellose sodium are weighed and added. The following table shows composition of group B.

3.3. Group C

In this group we are using sodium starch glycolate and croscarmellose sodium both as superdisintegrants. At first mannitol and microcrystalline cellulose are weighed accurately and incorporated in motor and pistor, then titrate in clock wise direction. Then sodium saccharine, sodium starch glycolate and croscarmellose sodium are weighed and added. The following table shows composition of group C.

Table 3: Formulation of group B

Name	*F1(mg)*	*F2(mg)*	*F3(mg)*	*F4(mg)*
Ondansetron hydrochloride	8	8	8	8
Sodium starch glycolate	_	_	_	_
Croscarmellose sodium	_	10	20	30
Microcrystalline cellulose	330	320	310	300
Mannitol	50	50	50	50
Sodium saccharine	5	5	5	5
Magnesium state	4	4	4	4

Table 4: Formulation of group C

Name	*F1(mg)*	*F2(mg)*	*F3(mg)*	*F4(mg)*
Ondansetron hydrochloride	8	8	8	8
Sodium starch glycolate	_	10	20	30
Croscarmellose sodium	_	10	20	30
Microcrystalline cellulose	330	320	310	300
Mannitol	50	50	50	50
Sodium saccharine	5	5	5	5
Magnesium state	4	4	4	4

4. Punching of Tablet

There are different types of machines are available for punching of tablet. Accurately weighed powder is filled in the block hole of tablet then powder is punched tablets are formed.

Figure 1: DBB.B. multitooling machine

Lab press DBB.B multitooling machine is used for punching of tablet is shown in figure 1. The standard size of tablet diameter is 8mm and weight is 400 mg.

5. Evaluation of tablets

5.1. Uniformity of weight (or weight variation)

Ten tablets were selected from each group and batch at a random and average weight is determined. Then individual tablets were weighed and the individual weight was compared with an average weight.

5.2. Wetting volume

The tablets are placed in the center of petri dish and with the help of 5ml pipette, distilled water is added drop wise on the tablet. The volume required to completely disintegrate the tablet is noted as wetting volume.

5.3 In-vitro disintegration time

The disintegration time is measured by using stirrer method. The vessel is filled with 500 ml of water maintained at 37 c. The stirrer is rotated at 100 revolutions per minute. The tablet is placed inside and disintegration time is recorded for each group.

5.4. In-vivo disintegration time

Measurements of disintegration time in mouth were carried out in four volunteers. After the mouth rinsed with purified water. One tablet is held in mouth until the tablet disintegrated without chewing and then spat out and the mouth is rinsed again. The disintegration time is recorded for each group. The systematic flow chart for the disintegration mechanism of FDT is shown in figure 2.

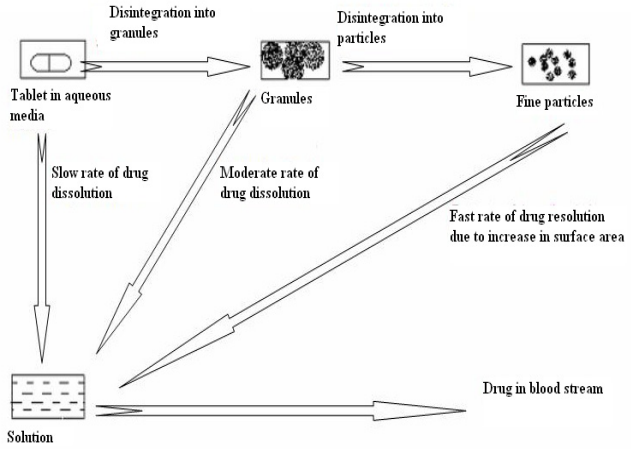

Figure 2: Flow chart of disintegration mechanism of FDT

5.5. Hardness of tablet

The tablet crushing load, which is the force required to break a tablet by compression in the radial direction is determined using hardness taster. From each batch of group A, B, C one tablet is placed in the tester and press manually and hardness is recorded. The following figure is the hardness tester

5.6 Friability test of tablet

Friability of tablets were measured by using friabilator. Friability is evaluated from the percentage weight of loss of 10 tablets tumbled in a friabilator at 25 rpm for 4 minutes. The tablets were dedusted, and loss in weight caused by fracture or abration is recorded as percentage weight loss. Friability below 1% is acceptable.

6. Result and Discussions

The present investigation is undertaken to formulate and evaluate oro dispersible tablets of ondansetron hydrochloride by direct compression method using sodium starch glycolate and croscarmellose sodium as superdisintegrants. Superdisintegrants are generally used by formulation scientists for developing ODTS or for improvement of solubility for active pharmacitical ingredients. The primary requirement of both dosage forms is quicker disintegration. The results for evaluation of different batches of ondansetron hydrochloride tablets prepared by direct compression method are shown in following tables from 5 to 7.

The weight variation occurred between all batches differences are 2-3 mg which were well within the acceptable limit of uncoated tablets as per united state pharmacopeia. The wetting volume is important to check for minimum volume of water required for wetting of tablets. The wetting volume required for group c 57-79 ml which shows very small amount of water is required for wetting of tablet. It has been reported that wetting volume is closely related to inner structure of the tablets and the hydrophilicity of the excipients.

It is well known that the tablets were higher crushing strength shows longer disintegration time hence the hardness is determined and fount in the range of 3.0 – 3.3 kg/cm3 and friability is observed between 0.32 to 0.7, which is shown in tables 5-7, which is less than 1 indicating good mechanical integrity and strength of prepared tablets. Thus, hardness and friability data indicates good mechanical resistance of tablet.

In-vitro and In-vivo dispersion for different batches is 72-93 seconds and 57-99 seconds respectively. The tablet formulation containing Sodium starch glycolate and croscarmellose sodium alone at low concentration (10 mg/tablet) Shows higher values of 54 to 73 seconds and 72 to 90 seconds for in-vitro and in-vivo disintegration time.

Thus these results indicate that ondansetron hydro chloride tablet would disintegrate almost instantaneously when they will come in contact with even slight quantity of saliva in the mouth.

Table 5: Result for group A

Serial no	*Batches*	*Hardness(kg/cm2)*	*Friability*
1	F1	3.2	0.32
2	F2	3.2	0.46
3	F3	3.0	0.40
4	F4	3.0	0.36

Table 6: Result for group B

Serial no	*Batches*	*Hardness(kg/cm2)*	*Friability*
1	F1	3.2	0.38
2	F2	3.1	0.42
3	F3	3.1	0.63
4	F4	3.2	0.54

Table 7: Result for group C

Serial no	*Batches*	*Hardness(kg/cm2)*	*Friability*
1	F1	3.1	0.69
2	F2	3.0	0.71
3	F3	3.0	0.58
4	F4	3.1	0.63

7. Conclusion

- Fast dispersing tablets of ondansetron hydrochloride were prepared by direct compression method using SSG, croscarmellose sodium and combination of both is used as a super disintegrants.
- The tablets disintegrated rapidly in oral cavity and had acceptable hardness and friability.
- The FDT's of ondansetron hydrochloride showed release depending on the concentration of super disintegrates.
- Tablet dimensions, weight, breaking force have no significant difference between tablets with different disintegrants.
- In vitro drug release from tablets shows significantly improved drug dissolution.

- It concluded that superdisintegrants based FDT of ondansetron would provide quick onset of action without need of water for swallowing or administration.

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