



International Journal of Pharmaceutics and Drug Analysis

Available at www.ijpda.com

ISSN: 2348:8948

Formulation and evaluation of triazolam odt's by direct compression for selection & optimization of super disintegrates

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Article History	Abstract
<p>Received on: 17-01-2021 Revised On : 18-02-2021 Accepted on : 27-02-2021</p>	<p>Oral Disintegrating Tablets of Triazolam were formulated with an aim to improve the versatility, patient compliance, and accurate dosing. The formulations were developed with an objective to use by the pediatric and geriatric patients. Triazolam Oral Disintegrating Tablets were prepared by direct compression method using cross povidone, croscarmellose sodium, sodium starch glycolate and combinations of CP+CCS, and CP + SSG as super disintegrates exhibited good pre-formulation and tableting properties of three super disintegrates, the formulation contained combination of CP + CCS showed better performance in terms of disintegration time when compared to other formulations. Order of the super disintegrates activity is as follows.</p> $(CP + CCS) > (CP + SSG) > CP > CCS > SSG$ <p>The formulation F15 was found to be the best among all twenty Triazolam ODT formulations because it has exhibited faster disintegration time (17.66 sec) when compared to the other formulations and it showed 99.87±0.18% drug release at the end of 25 min. Triazolam Oral Disintegrating Films were prepared by solvent casting method using different grades of Hydroxypropyl Methyl Cellulose like HPMC – E15, HPMC – 5cps, HPMC – 50cps. Based on disintegration and dissolution results it was concluded that the formulation F15 contained CP 5% + CCS 5% was the best formulation among all other formulations.</p> <p>Keywords: Triazolam, Oral Disintegrating.</p>
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<p>DOI:https://doi.org/10.47957/ijpda.v9i1.456</p>	

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Introduction

Oral disintegrating tablets (odt)

Oral administration is the most popular route about 50-60% of total dosage forms are administered due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly patient compliance. Solid oral delivery

systems do not require sterile conditions and are therefore less expensive to manufacture [1]. One important drawback of solid dosage forms is the difficulty in swallowing (dysphasia) or chewing in some patient's particularly pediatric and geriatric patients [2]. The problem of swallowing is common phenomenon in geriatric patient due to fear of choking, hand tremors,

dysphasia and in children's due to underdeveloped muscular and nervous systems and in schizophrenic patients resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. Difficulties in swallowing of tablet and capsule also occur when water is not available, in diarrhea, coughing during the common cold, allergic condition and bronchial infection.

Oral fast dissolving drug delivery system (OFDDS) is one such novel approach to increase consumer acceptance by virtue of rapid disintegration, self-administration without water or chewing. Orally disintegrating tablets (ODT) are solid unit dosage forms like conventional tablets, but are composed of super disintegrates, which help them to disintegrate the tablet rapidly in saliva without the need to take it water. Orally disintegrating tablets (ODT) are not only indicated for people who have swallowing difficulties, but also are ideal for active people.

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." Orally disintegrating tablets are also called as mouth-dissolving tablets, fast disintegrating tablets, fast dissolving tablets, orodispersible tablets, porous tablets, quick dissolving tablet [4]. Recently European pharmacopoeia also adopted the term 'orodispersible tablet' as a tablet that is to be placed in the mouth where it disperses rapidly before swallowing [3]. Despite various terminologies used, orally disintegrating tablets are here to offer unique form of drug delivery with many advantages over the conventional dosage forms.

Selection of Super disintegrants [6]

Although Super disintegrants primarily affect the rate of disintegration, but when used at high levels they can also affect mouth feel, tablet hardness and friability. Hence, various ideal factors to be considered while selecting appropriate super disintegrates for a particular formulation should.

- Produce rapid disintegration (hydrophilic) when tablet meets saliva in the mouth.
- Be compactable enough to produce less-friable tablets.
- Produce good mouth feel to the patient. Thus, small particle size is preferred to achieve patient compliance.
- Have good flow since it improves the flow ability of the total blend.

Formulation aspects in developing ODTs [3]

Orally disintegrating tablets are formulated by utilizing several processes, which differ in their methodologies and ODTs formed vary in various properties such as

1. Mechanical strength of tablets
2. Taste and mouthfeel
3. Swallow ability
4. Drug dissolution in saliva
5. Bioavailability
6. Stability

TECHNIQUES IN PREPARATION OF ODDS [7,11]

1. Freeze drying or Lyophilization.
2. Spray drying
3. Molding
4. Phase transition process
5. Melt granulation.
6. Sublimation
7. Mass extrusion
8. Cotton candy process
9. Direct compression
10. Nanonization
11. Effervescent method.

Direct Compression

Direct compression is the easiest way to manufacture tablets and therefore, ODTs. The great advantage of direct compression is low manufacturing cost. It uses conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Moreover high doses can be accommodated and final weight of tablet can easily exceed that of other production methods [16].

The direct compression tablet's disintegration and Solubilisation are based on the single or combined action of disintegrates, water-soluble excipients, and effervescent agents. The disintegration time is, in general, satisfactory, although the disintegrating efficacy is strongly affected (and limited) by tablet size and hardness. Large, hard tablets can have a disintegration time greater than that usually required for ODTs. As a consequence, products with optimal disintegration properties often have a medium-small size (weight) and/or a low physical resistance (high friability and low hardness) are formulated but breakage of tablet edges during handling, the presence of deleterious powder in the blistering phase, and tablet rupture during the opening of the blister alveolus, all result from insufficient physical resistance [16].

In many cases the disintegrates have a major role in the disintegration and dissolution process of ODTs made by direct compression. The choice of a suitable type and an

optimal amount of disintegrates is paramount for ensuring a high disintegration rate. The addition of other formulation components such as water soluble excipients or effervescent agents can further enhance dissolution or disintegration properties. The understanding of disintegrates properties and their effect on formulation has significantly advanced during the last few years, particularly regarding so called super disintegrates.

This technique can now be applied to preparation of ODT because of the availability of improved excipients especially super disintegrates and sugar based excipients.

(a) Super disintegrates.

In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrates principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration⁹.

(b) Sugar Based Excipients

This is another approach to manufacture ODT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltitol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and pleasing mouthfeel. Mizumoto et al have classified sugar-based excipients into two types on the basis of molding and dissolution rate. Type 1 saccharides (lactose and mannitol) exhibit low mouldability but high dissolution rate. Type 2 saccharides (maltose and maltitol) exhibit high mouldability and low dissolution rate [9].

Role of superdisintegrants in ODT

The basic approach in development of ODTs is use of disintegrant. Disintegrant plays an important role in the disintegration and dissolution of ODT. It is essential to choose a suitable disintegrant, in an optimum concentration so as to ensure quick disintegration and high dissolution rates. Super disintegrant provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of super disintegrant, the wetted surface of the carrier increases; this promotes the wettability and dispersibility of the system, thus enhancing the

disintegration and dissolution. Care should be taken to taken while selecting concentration of the Superdisintegrants. Superdisintegrants are selected according to critical concentration of disintegrant. Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the super disintegrant, whereas if concentration of super disintegrant is above critical concentration, the disintegration time remains almost constant or even increases. Common disintegrants used in this formulation are croscarmellose sodium (Vivasol, Ac-Di-Sol), cross povidone (Polyplasdone), caramellose (NS-300), caramellose calcium (ECG-505), sodium starch glycolate (SSG) etc. Recently few ion exchange resins (e.g., Indian 414) are found to have super-disintegrant property and are widely used in pharmaceutical industry.

Mechanism of superdisintegrants [7]

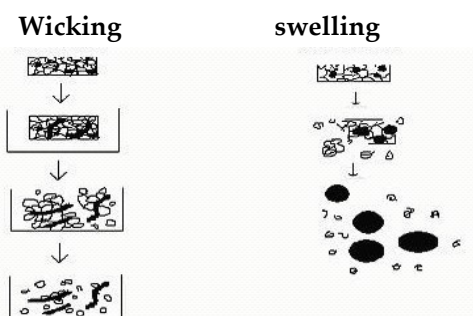
There are major mechanisms for tablets disintegration as follows.

Swelling [7,9]

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

Porosity and capillary action (Wicking) [7,9]

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipient and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.



Due to disintegrating particle/particle repulsive forces [7,9]

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swelling' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non-swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

Due to deformation [7,9]

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water.

Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

Materials & methods

S.No	Name of the Drug	Name of the Company
1.	Triazolam	HETERO DRUGS -HYD
2.	Cross povidone	HETERO DRUGS -HYD
3.	Cross carmellose sodium	HETERO DRUGS -HYD
4.	Sodium starch glycolate	HETERO DRUGS -HYD
5.	Avicel-PH 102	HETERO DRUGS -HYD
6.	Sodium stearyl fumarate	HETERO DRUGS -HYD
7.	PearlitoSD-200	HETERO DRUGS -HYD
8.	Sodium saccharine	HETERO DRUGS -HYD

9.	Orange flavour	HETERO DRUGS -HYD
10.	Methanol	HETERO DRUGS -HYD
11.	Potassium dihydrogen Ortho phosphate purified	HETERO DRUGS -HYD
12.	Sodium hydroxide	HETERO DRUGS -HYD
13.	Eosin(dye)	HETERO DRUGS -HYD

Formulation and evaluation of oral disintegrating tablets of triazolam

Formulation design

Triazolam ODTs were prepared using direct compression technique. Direct compression technique is a convenient method, but the excipients used in this method are costlier when compared to the excipients used in the wet granulation technique.

Different formulations of Triazolam ODTs were designed to be prepared by direct compression technique using three super disintegrants, (Cross povidone, Croscarmellose sodium and Sodium starch glycolate). Super disintegrant is varied with 4 different concentrations, (i.e., 3, 6, 9, 12% respectively) keeping all other ingredients constant, there are assigned with formulation codes shown.

General formulation

A formula is set using following ingredients.

Drug	Triazolam
Disintegrant :	Cross povidone / Croscarmellose sodium/Sodium starch glycolate
Bulking agent :	Pearlitol SD 200, Avicel pH102
Sweetening agent :	Sodium saccharine
Flavouring agent :	Orange
Lubricant :	Sodium Stearyl fumarate
Total table weight was set to be 1000mg. Punch size is set to be 5 mm s/c.	

Formulation codes of ODT

Disintegrant used	Concentration (%)	Formulation code
Cross povidone	3	F1
	6	F2
	9	F3

	12	F4
Croscarmellose sodium	3	F5
	6	F6
	9	F7
	12	F8
Sodium starch glycolate	3	F9
	6	F10
	9	F11
Cross povidone + croscarmellose sodium	12	F12
	6 (3:3)	F13
	8 (4:4)	F14
	10 (5:5)	F15
Cross povidone + sodium starch glycolate	12 (6:6)	F16
	6 (3:3)	F17
	8 (4:4)	F18
	10 (5:5)	F19
	12 (6:6)	F20

Procedure

All the required ingredients were passed through 40 mesh to get uniform size particles and weighed accurately. Whole amount of drug, pearlitol SD 200, Avicel pH 102, sodium saccharine and flavour except lubricant were mixed in the increasing order of their weights in a mortar. To this mixture talc and sodium Stearyl fumarate were added. The final mixture was shaken manually for 5-10 minutes in a plastic bag. This powder was passed through the hopper of 16 station rotary tableting machine and punched into tablets using 5 mm s/c. The process is similar for all the formulations, which are prepared by direct compression technique.

Various *In-vitro* tests performed are

- Weight variation test
- Thickness measurement
- Hardness and Friability
- Assay
- Wetting time and Water absorption ratio.
- Disintegration Time
- Dissolution test

Results & discussion

Oral Disintegrating Tablets

Using various disintegrants like Cross povidone, Croscarmellose sodium, Sodium starch glycolate tablets were prepared along with other additives. Direct compression method was used for the preparation of tablets. A total number of 20 formulations were prepared and evaluated.

Formulae of Triazolam ODTs prepared by direct compression method with various super disintegrants.

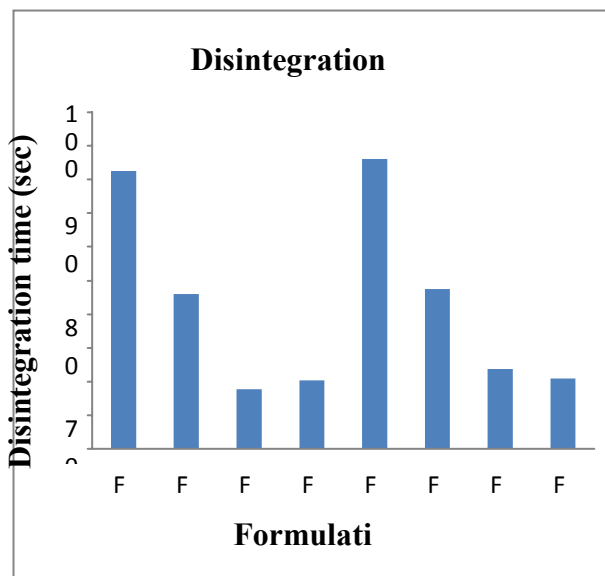
Ingredients	Super disintegrants concentration (%) of Cross povidone/ Croscarmellose Sodium/ Sodium Starch Glycolate			
	3 %	6 %	9 %	12 %
Triazolam	1 5	1 5	1 5	1 5
Super disintegrants	9	1 8	2 7	36
Avicel PH 102	5 3	4 2	3 3	22
Pearlitol SD200	1 0	1 0	1 0	10
Sodium saccharin	1 0	1 0	1 0	10
Orange flavor	2	2	2	2
Sodium Stearyl fumarate	0 5	0. 5	0 5	0.5
Talc	0 5	0. 5	0 5	0.5
Total weight (mg)	1 0 0	1 0 0	1 0 0	1 0 0

Tableting characteristics of Triazolam ODTs prepared with combination of Super disintegrants.

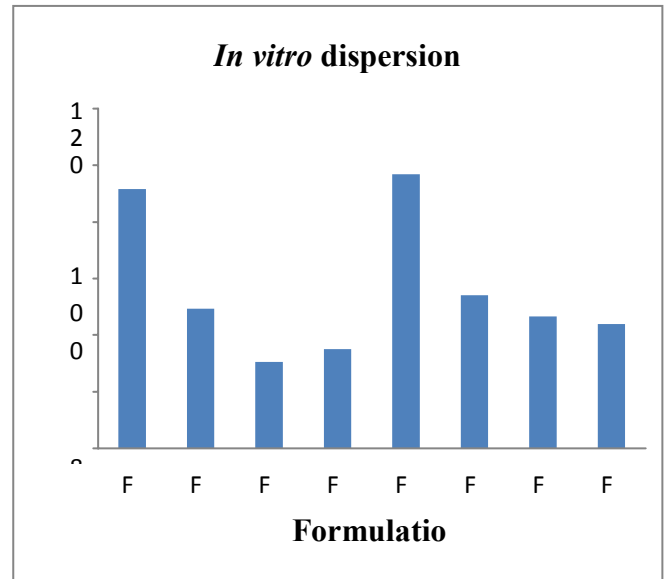
Formulation	Weight (mg)	Drug Content (%)	Hardness (kg/cm ²)	Friability (%)	Thickness (mm)
F13	80.3± 1.18	98.56 ±0.49	3.19± 0.05	0.47	3.86±0.0 34
F14	79.3± 0.53	98.61 ±0.60	3.16± 0.04	0.52	3.86±0.0 23

F15	80.1± 0.75	98.98 ±0.56	3.10± 0.10	0.63	3.87±0.0 44
F16	80.3± 0.86	99.03 ±0.58	3.05± 0.09	0.58	3.89±0.0 51
F17	79.1± 0.84	97.75 ±0.69	3.15± 0.04	0.58	3.85±0.0 29
F18	78.8± 0.56	98.76 ±0.56	2.92± 0.08	0.53	3.88±0.0 46
F19	79.6± 0.60	99.08 ±0.29	3.00± 0.09	0.51	3.86±0.0 25
F20	80.0± 0.75	98.86 ±0.39	3.12± 0.12	0.55	3.84±0.0 34

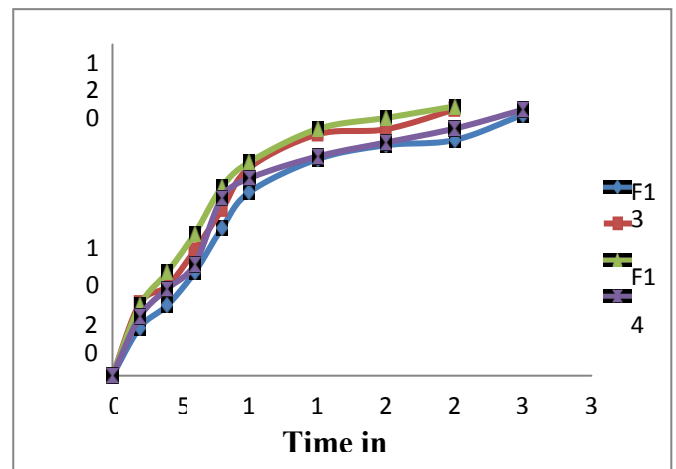
Formula tion	Wettin g time (sec)	In vitro dispersion time (sec)	Disintegr ation time (sec)	Water absorption Ratio (%)
F13	19.33 ±0.51	91.66 ±1.21	82.5±1.04	59.49
F14	14.33 ±0.51	49.33 ±1.03	46±0.89	56.59
F15	11.16 ±0.75	30.66 ±0.81	17.66±0.5 1	57.08
F16	12.5± 0.54	35.16 ±0.75	20.33±0.8 1	58.72
F17	19.1± 0.75	96.83 ±0.40	86.16±0.7 5	57.95
F18	14.83 ±0.75	54.16 ±1.72	47.5±1.04	60
F19	11.5± 0.54	46.66 ±0.81	23.66±0.5 1	61.50
F20	13± 0.89	43.83 ±0.75	20.83±1.1 6	58.24



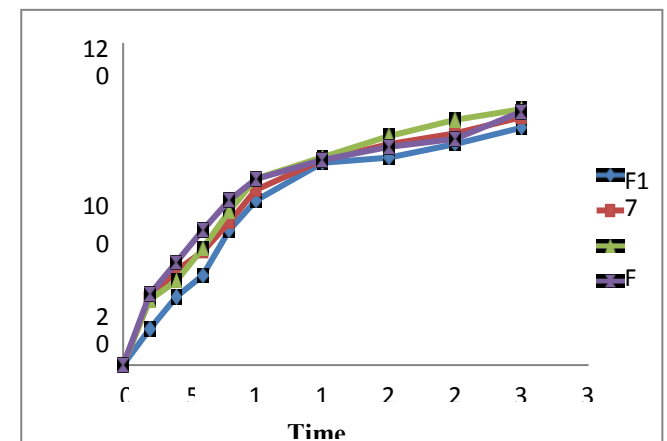
Graphical representation of disintegration times of Triazolam ODTs prepared by varying concentrations of combination of Super disintegrants.



Graphical representation of disintegration times of Triazolam ODTs prepared by varying concentrations of combination of Super disintegrants.



Graphical representation of Cumulative percent Triazolam released from ODTs containing varying concentrations of CP +CCS



Graphical representation of Cumulative percent lisinopril released from ODTs containing varying concentrations of CP +SSG

To achieve such a formulation, most of the excipients selected must be water soluble by nature. Pearlitol SD 200 is a directly compressible grade of mannitol with good flow properties and gives a refreshing or cooling effect in the mouth due to its negative heat of solution. This excipient was used as a bulking agent to achieve the desired tablet weight. Avicel 102 was included in the formulation mainly as a disintegrant at the concentrations used and to some extent as diluents. This grade of microcrystalline cellulose is granular in nature and thus displays excellent flow. To impart pleasant taste and mouth feel sodium saccharin and orange were included as sweetening and flavoring agents respectively. Sodium stearyl fumarate was employed as a lubricant instead of magnesium stearate to overcome the metallic taste of the latter and also due to its water-soluble nature.

Cross povidone polymers are densely cross-linked homo polymers of N – vinyl 2 – pyrrolidone's. Their porous particle morphology helps to rapidly wick liquids into the tablet by capillary action to generate the rapid volume expansion and hydrostatic pressures that cause tablet disintegration. In addition to its unique particle size and morphology, cross povidone is non-ionic, and its disintegration performance will neither be influenced by pH changes in the gastrointestinal tract nor will they complex with ionic drug actives. They can also be used as solubility enhancers resulting in a faster dissolution rate without forming gels.

Croscarmellose sodium is cross-linked carboxymethyl cellulose sodium which can be used at concentrations of up to 5% as a disintegrant. Its unique fibrous nature gives excellent water wicking capabilities and crosslinking makes it hydrophilic and highly absorbent material, resulting in its swelling properties. It rapidly swells up to 4 – 8 times its original volume on contact with water. Like cross povidone, it is also used as a dissolution aid, hence the name Ac-Di-Sol (accelerates dissolution).

Sodium starch glycolate is a sodium salt of carboxymethyl ether of starch, usually employed at concentrations between 2 – 8% although an optimum concentration of 4% may be sufficient in many cases. Disintegration occurs by rapid uptake of water followed

by rapid and enormous swelling, which is its primary mechanism of action. It (exploitable) swells up to 300 times its original volume in water.

In all formulations, tablet weight and thickness were within mean $\pm 7.5\%$ and mean $\pm 5\%$ respectively. The weight variation in all the twenty formulations was found to be 78.5 mg to 80.4 mg, which was in pharmacopoeia limits. The thickness varies between 3.84 to 3.92 mm. Friability values were less than 1% in all cases. Hardness of all the tablets was maintained at 2.9 to 3.19 kg for all the formulations as mentioned before. Assay was performed and percent drug content of all the tablets were found to be between 97.75% and 99.36% of Triazolam, which was within the acceptable limits.

Wetting time was determined for all the formulations. The values lie between 11.16 ± 0.75 to 57.33 ± 0.81 . The variability in wetting time for different formulations may be due to the changes in the compaction which cannot be controlled during tablet preparation and the type of the disintegrant affected the wetting of the tablets. On comparing the Superdisintegrants the formulations containing cross povidone + croscarmellose sodium and cross povidone + sodium starch glycolate take less wetting time than the other formulations containing single Superdisintegrants. Water absorption ratio ranged from 56.59 % – 67.54 %. Cross povidone and croscarmellose sodium perform their disintegrating action by wicking through capillary action and fibrous structure, respectively with minimum gelling. The relative ability of the various disintegrants to wick water into the tablets was studied. After contact with water the tablets containing sodium starch glycolate swelled, the outer edge appeared gel like. Tablets containing cross povidone quickly wick water and were hydrated, but were soft as compared with tablets prepared with croscarmellose sodium and sodium starch glycolate. The center of the tablets with sodium starch glycolate and croscarmellose sodium remained dry and hard.

Disintegration time is considered to be an important criteria in selecting the best ODT formulation. The *in vitro* disintegration time for all the twenty formulations varied from 17.66 ± 0.51 to 17.83 ± 1.16 seconds. The rapid disintegration was seen in the formulations containing cross povidone and formulations containing combination of Superdisintegrants (CP+ CCS, CP + SSG). This is due to rapid uptake of the water from the medium, swelling and burst effect. It is also noticed that as the disintegrant concentration was increased from 9 to 12% the time taken for disintegration was reduced.

The disintegration time of formulation (F15) containing 5% CP + 5% CCS was found to be lower (17.66±0.51) and was selected as the best ODT formulation among all the 20 formulations.

In vitro dispersion is a special parameter in which the time taken by the tablet for complete dispersion is measured. The time for all the twenty formulations varied between 30.66±0.81 and 259.83±1.47 sec.

The development of dissolution method for ODTs is almost similar to the approach taken for conventional tablets until they utilize the taste masking. The taste masking aspect greatly influences dissolution method development, specifications, and testing. Several factors like varied thickness and pH dependent solubility of drug particle coating influence dissolution profiles of ODTs containing taste masked actives. Since Triazolam is not bitter in taste, the metallic taste of drug was masked by using sweeteners and flavors. It has been reported that USP type II apparatus with a paddle speed of 50 rpm is commonly used for ODT formulations. Slower paddle speeds are utilized to obtain good profiles as these formulations disintegrate rapidly.

In vitro dissolution studies of the prepared ODTs was performed in pH 6.8 phosphate buffer using USP dissolution apparatus type 2. The dissolution rate was found to increase linearly with increasing concentration of Superdisintegrants. Formulations F1, F2, F3 and F4 which contained increasing concentrations of cross povidone have recorded drug release 95.78%, 96.85%, 97.96 and 98.99% respectively within 20 to 30 min. Formulations F5, F6, F7 and F8 which contained increasing concentrations of croscarmellose sodium have recorded drug release 89.53%, 92.36%, 94.46% and 95.43% respectively, at the end of 30 min. Formulations F9, F10, F11 and F12 which contained increasing concentrations of sodium starch glycolate have recorded drug release 85.4%, 88.45%, 90.4% and 92.38% respectively, at the end of 30 min. Formulations F13, F14, 15 and F16 which contained increasing concentrations of combination of CP + CCS have recorded drug release 94.5%, 96.52%, 99.87% and 96.38% respectively, at the end of 25 to 30 min. Formulations F17, F18, F19 and F20 which contained increasing concentrations of combination of CP + SSG have recorded drug release 88.56%, 92.5%, 95.48% and 94.51% respectively, at the end of 30 min.

Summary & conclusion

Oral Disintegrating Tablets of Triazolam were formulated with an aim to improve the versatility,

patient compliance and accurate dosing. The formulations were developed with an objective to use by the pediatric and geriatric patients. Triazolam Oral Disintegrating Tablets were prepared by direct compression method using cross povidone, croscarmellose sodium, sodium starch glycolate and combinations of CP+CCS, and CP + SSG as Super disintegrants exhibited good Preformulation and tableting properties, of three Super disintegrants, the formulation contained combination of CP + CCS showed better performance in terms of disintegration time when compared to other formulations. Order of the Super disintegrants activity is as follows

(CP + CCS) > (CP + SSG) > CP > CCS > SSG

The formulation F15 was found to be the best among all the twenty Triazolam ODT formulations because it has exhibited faster disintegration time (17.66 sec) when compared to the other formulations and it showed 99.87±0.18% drug release at the end of 25 min. Triazolam Oral Disintegrating Films were prepared by solvent casting method using different grades of Hydroxy Propyl Methyl Cellulose like HPMC – E15, HPMC – 5cps, HPMC – 50cps. Based on disintegration and dissolution results it was concluded that the formulation F15 contained CP 5% + CCS 5% was the best formulation among all other formulations. FTIR study showed no drug excipient interaction. The metallic taste of the drug was masked by Sodium saccharin, and Orange flavor.

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