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FORMULATION AND EVALUATION OF ORAL DISINTEGRATING TABLETS OF ETORICOXIB USING VARIOUS SUPERDISINTEGRANTS

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ABSTRACT

The present study aimed to design and evaluation studies on oral disintegration tablets of etoricoxib using various superdisintegrants [1]. The concept of fast 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 fast dissolving tablets when put on tongue these tablets disintegrate and dissolve rapidly in saliva without need of drinking water [2]. The faster the drug disintegrates in to solution, the quicker the absorption and onset of clinical effect. Preformulation studies such as Angle of repose, Bulk density, Tap density, Compressibility index and Hausner's ratio were carried out to find the flow properties of the powder which are very important parameters in the formulation of tablets. Preformulation results reveal that the flow properties of the active pharmaceutical ingredient were found to be excellent as per IP limits. To perform drug-polymer compatibility FT-IR studies were carried out and observed that there was no interaction between the APl and excipients [3]. Nine formulations of disintegration tablets of etoricoxib (F1-F9) were prepared by using direct compression technique with various compositions of superdisintegrants and the prepared formulations were evaluated for Hardness, weight variation, Thickness, friability, wetting time, assay, disintegration time and dissolution parameters. Among all the formulations F9 has found to be the optimized formulation with optimum hardness of 3 kg/m² and least disintegration time of 15 sec and has shown maximum in-vitro percentage release of 99.9 %.

KEYWORDS: *Etoricoxib, Oral Disintegration tablets, Fast Dissolving tablets, Superdisintegrants.*

INTRODUCTION

The most important drug delivery route is undoubtedly the oral route. It offers advantages of convenience of administration and potential manufacturing cost savings. Drugs that are administered orally, solid oral dosage forms in general and tablets in particular represent the preferred class of product [4]. Today drug delivery companies are focusing on solid oral drug delivery systems that offer greater patient compliance and effective dosages. Some of the problems associated with tablets particularly by paediatric and geriatric patients, 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 [5]. 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 offer an advantage for populations who have difficulty in swallowing. ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population. 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 dosage forms as ODTs. Recently, European Pharmacopoeia has used the term orodispersible tablet for tablets that disperses readily and within 3 min in mouth before swallowing. 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 [6].

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METHODOLOGY

Pre Formulation Parameters:

Angle of Repose:

The internal angle between the surface of the pile of blend and the horizontal surface is known as the angle of repose.

Method:

The Angle of repose was known by passing the blend through a funnel fixed to a burette stand at a particular height (4 cm). A graph paper was placed below the funnel on the table. The height and radius of the pile was measured. Angle of repose of the blend was calculated using the formula.

$$Angle\ of\ repose = \tan^{-1}\left(\frac{Height\ of\ the\ pile}{Radius\ of\ the\ pile}\right)$$

Bulk Density:

Bulk density is the ratio of given mass of powder and its bulk volume. It was determined by transferring an accurately weighed amount of powder sample to the graduated cylinder with the aid of a funnel. The initial volume was noted. Ratio of weight of the sample to the volume it occupied was calculated.

$$Bulk\ density = \frac{Mass\ of\ the\ blend\ (W)}{Untapped\ volume\ (Vo)}$$

Tapped Density:

Tapped density was measured by transferring a known quantity of blend into a graduated cylinder and was placed on the tapped density apparatus. The initial volume was noted. The apparatus was set for 500, 750 and 1250 taps. The tapped density was determind as the ratio of mass of the blend to the tapped volume.

$$Tap\ density = \frac{Mass\ of\ the\ blend\ (W)}{tapped\ volume\ (Vf)}\ gm/ml$$

Compressibility Index:

It is measured by tapped density apparatus for 500, 750 and 1250 taps for which the difference should be not more than 2%. Based on the apparent bulk density and tapped density the percentage compressibility of the blend was determined using the following formula.

$$\%Compressability = \frac{(Tap\ density - Bulk\ denisty)}{Tap\ density} \times 100$$

Hausner Ratio:

It indicates the flow properties of the powder. The ratio of tapped density to the bulk density of the powders is called Hausner ratio.

$$Hausner\ ratio = \frac{Tapped\ density}{Bulk\ density}$$

Drug Excipient Compatibility studies:

Standard calibration curve of the Etoricoxib:

25mg of the dug was dissolved in the 50ml of 0.1N Hcl and sonicated for few minutes and further diluted to 100ml with 0.1N Hcl. From this above solution futher dilutions were carried out to obtained 2, 4, 6, 8, 10 µg/ml using methanol. The absorbance of the above concentration was measured at 235 nm using UV spectroscopy.

Fourier Transform Infrared Spectroscopy (FT-IR):

Infrared radiation can be worked in two different ways, either the radiation is absorbed by the sample or it can passed through the sample. FT-IR results represent the molecular absorption and transmission of the sample which gives a fingerprint image of the sample. So for different samples it carries unique spectra and gives the blue print of the sample. This characterization is very useful for analysis of number of samples [7]. In FTIR analysis sample has been analysed in the wave number between 4000-400 cm^{-1}.KBr pallets is prepared for the FTIR analysis. KBr is added with the sample and finally pallet has been formed and submitted to the FTIR analysis. Potassium bromide (KBr) is the commonest alkali halide used in the pellets due to its high transparency. FT-IR analysis can be used for the identification of unknown materials, determination of quality and compatibility of the sample in a mixture.

Formulation of Etoricoxib tablets:

As the amount of drug substance weighed may not be equivalent to the desired weight (because of the presence of moisture).Therefore the quantity of substance to be weighed was calculated as follows;

$$\text{Amount of Drug to be taken} = \frac{\text{Strength of the tablet} \times 100 \times 100 \times \text{batch size}}{\text{Assay of the sample} \times (100 - \text{LOD}) 1000}$$

Table No. 1: Formulation Developmental Trails

Excipients /Formulations	F1	F2	F3	F4	F5	F6	F7	F8	F9
Etoricoxib	60	60	60	60	60	60	60	60	60
SSG	5	10	15	-	-	-	-	-	
CP	-	-	-	5	10	15	-	-	-
CCS	-	-	-	-		-	5	10	15
Mannitol	137.5	132.5	127.5	137.5	132.5	127.5	137.5	132.5	127.5
Talc	5	5	5	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5	5	5	5
PVP	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5
Total weight(mg)	200	200	200	200	200	200	200	200	200

Note: Quantities in mg

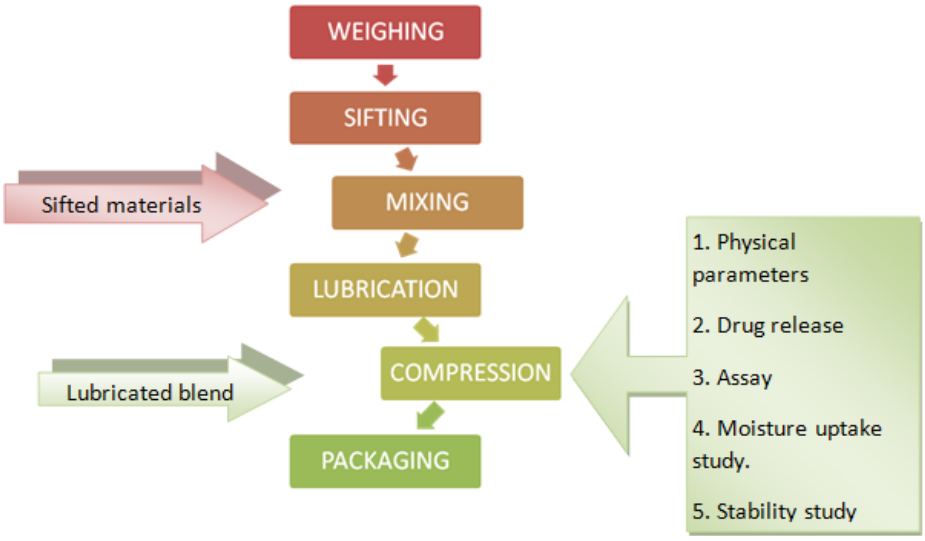


Fig. 1: Manufacturing Process by Direct Compression Technique

Post Compression Parameters:

Physical Appearance:

The physical appearance of the compressed tablets involves the measurement of a number of attributes like tablet shape, smoothness, chipping, cracks, surface texture, colour etc.

Thickness:

Thickness was determined for 20 pre-weighed tablets of each batch using a digital vernier scale and the average thickness was determined in mm**.** The tablet thickhness should be controlled within a ± 5% variation of a standard.

Weight Variation:

20 tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated. The tablets meet the USP specifications if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limits.

Table No. 2: IP limits for weight variation

Average weight of tablet (mg)	% difference
130 or less	10 %
From 130 to 324	7.5%
> 324	5%

Hardness Test:

The crushing load which is the force required to break the tablet in the radial direction was measured using a Schluenzier hardness tester. The hardness of 10 tablets was noted and the average hardness was calculated. It is given in kp or kg/cm^2.

Friability:

If the tablet weight is ≥ 650 mg 10 tablets were taken and initial weight was noted. For tablets of weight less than 650 mg the number of tablets equivalent to a weight of 6.5 g were taken. The tablets were rotated in the Roche Friabilator for 100 revolutions at 25 rpm. The tablets were dedusted and reweighed. The percentage friability should be not more than 1%w/w of the tablets is being tested.

The percentage friability is expressed as the loss of weight and is calculated by the formula:

$$\%Friability = \frac{(Intial\ weight\ of\ tab - Final\ weightof\ tab)}{Final\ weightof\ tab} \times 100$$

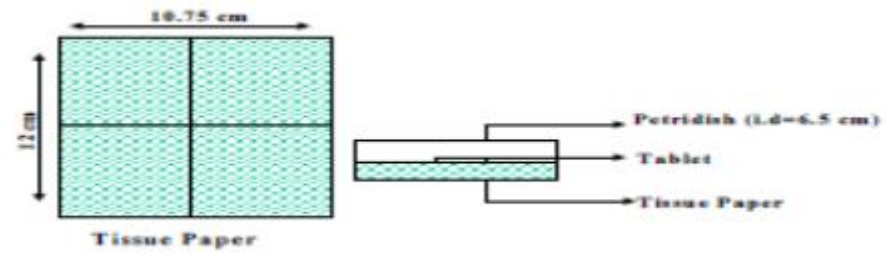
Disintegration Time:

Disintegration time is the time taken by the tablet to breakup into smaller particles. The disintegration test is carried out in an apparatus containing a basket rack assembly with six glass tubes of 7.75 cm in length and 2.15 mm in diameter, the bottom of which consists of a #10 mesh sieve. The basket is raised and lowered 28-32 times per minute in a medium of 900 ml which is maintained at 37±2^{0}C. Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments through the mesh (# 10) was considered as the disintegration time of the tablet. The disintegration time that patients can experience for oral disintegrating tablets ranges from 5 to 30seconds.

Wetting time and water absorption ratio:

Wetting time of dosage form is related to with the contact angle. Wetting time of the ODT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablets can be measured by using the simple procedure [8]. Five circular tissue papers of 10cm diameter are placed in a petridish. Ten milliliters of water soluble dye solution 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 the wetting time. For measuring water absorption ration the weight of the tablet before keeping in the petridish is noted (Wb). The wetted tablet from the petridish is taken and reweighed (Wa). The water absorption ratio,*R* can be the determined according to the following equation.

$$R = 100\ (Wa\text{-}Wb)\ /\ Wb$$



Simple Method for the Measurement of Wetting Time of a Tablet

Dissolution Studies:

The dissolution test was carried out in USP Apparatus Type II (paddle) with 0.1 N Hydrochloric acid as the dissolution medium. The samples were drawn at 5, 10, 15, 20 and 30 min. Fresh volume of the medium were replaced with the withdrawn volume to maintain the sink conditions. Samples withdrawn were analyzed for the percentage of drug released.

Dissolution Parameters:

Dissolution Apparatus : USP Apparatus Type II (Paddle)
Dissolution Medium : 0.1N Hydrochloric acid
Volume : 900 ml
Temperature : 37±2° C
Rpm : 50
Sampling Intervals (min) : 5, 10, 15, 20 &30min

RESULTS AND DISCUSSION

Pre-Formulation Study:

Table No. 3: Results of Pre Compression Parameters

S.No	BATCH NO	ETORICOXIB
1	Angle of repose	28.98 ± 0.13
2	Bulk density	0.463 ± 0.31
3	Tap density	0.509 ± 0.27
4	Compressibility index	9.03 ±0.63
5	Hausner ration	1.09 ± 0.12

Table No. 4: Calibration table of Etoricoxib

Concentration(µg/ml)	Absorbance at 242 nm
2	0.112
4	0.224
6	0.312
8	0.416
10	0.518
12	0.614
14	0.708

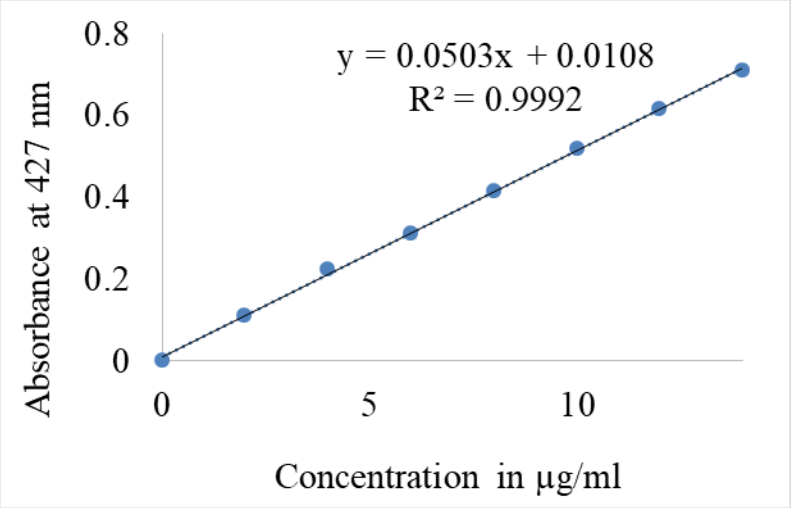


Fig. 2: Calibration graph of Etoricoxib

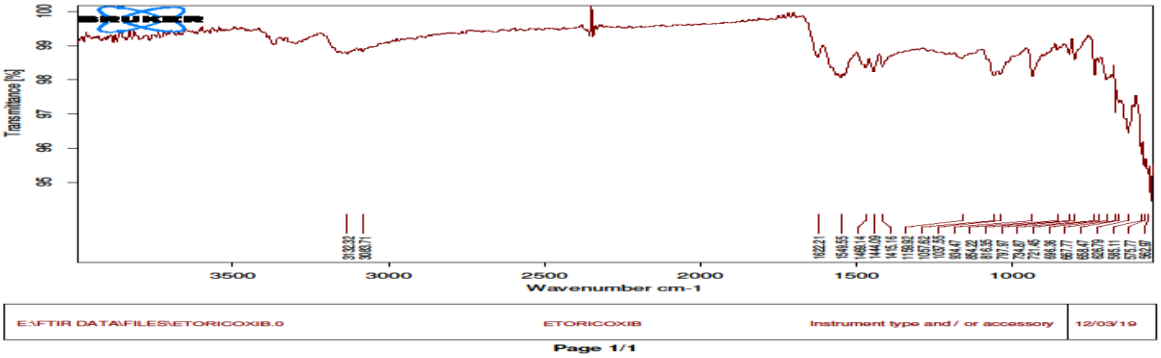


Fig. 3: FT-IR spectrum of Etoricoxib

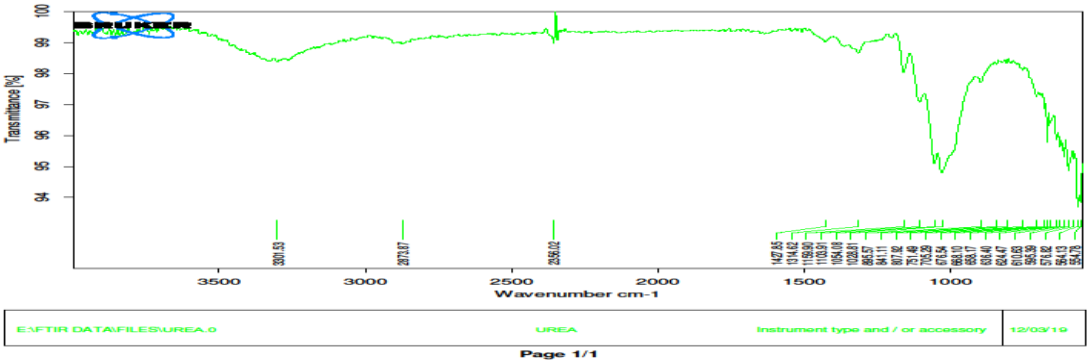


Fig. 4: FT-IR spectrum of Urea

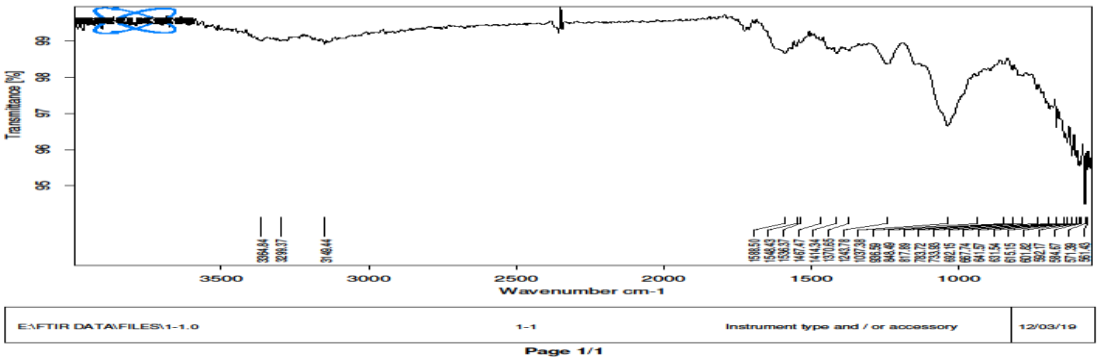


Fig. 5: FT-IR spectrum of Physical Mixture 1:1

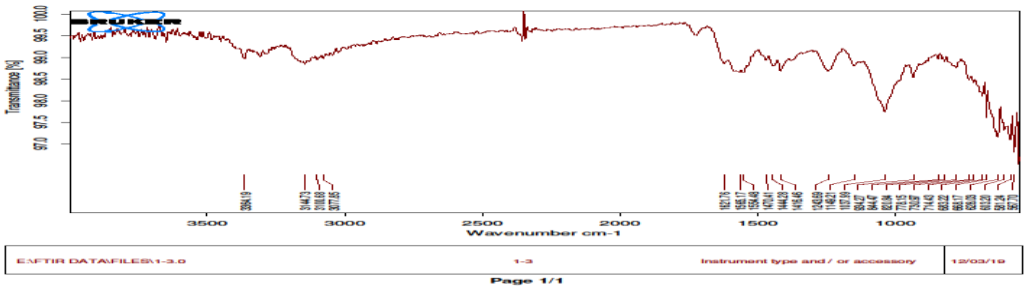


Fig. 6: FT-IR spectrum of Physical Mixture 1:3

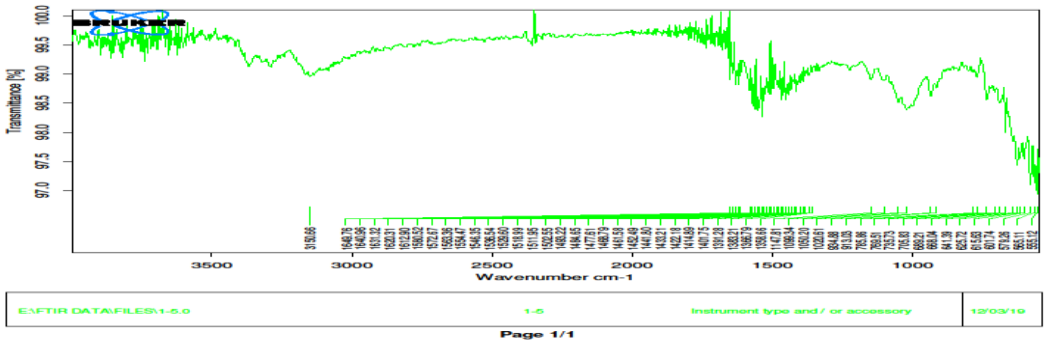


Fig. 7: FT-IR spectrum of Physical Mixture 1:5

Evaluation of Post Compression Parameters:

Table No. 5: Results of post compression parameters

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight variation	200±0.92	201±0.91	200±0.92	201±0.92	201±0.91	201±0.91	200±0.92	200±0.92	200±0.91
Friability	0.65	0.59	0.90	0.74	0.70	0.65	0.87	0.64	0.38
Hardness	4.26±0.68	4.12±0.94	4±0.53	3.82±0.54	3.7±0.62	3.6±0.37	3.4±0.37	3.36±0.37	3±0.32
Thickness	4.32±0.42	4.24±0.36	4.1±0.26	3.93±0.28	3.82±0.62	3.61±0.48	3.42±0.32	3.21±0.26	3.12±0.25
Wetting time	57±1.5	47±1.3	46±1.4	43±1.8	39±1.3	34±1.2	33±1.4	26±1.6	15±0.4
Disintegration time	46±1.1	45±1.4	40±1.7	35±1.3	31±2.6	35±3.8	22±4.2	20±1.2	15±0.9
Assay	93.6±0.99	93.8±0.98	94.2±1.0	94.6±0.91	95.1±0.98	93.2±0.98	93.8±0.92	98.3±092	99.9±0.89
Dissolution time									
5	89.2	89.8	91.2	91.7	91.9	92.3	92.3	92.9	93.5
10	91.6	91.9	92.6	92.8	93.8	94.2	94.6	94.9	95.6
15	92.2	92.6	92.8	93.1	93.2	94.4	94.6	95.2	96.2
20	94.4	94.6	95.1	95.3	95.6	96.1	96.2	96.3	96.8
25	96.2	96.5	96.8	96.9	97.1	97.3	97.6	97.8	98.6
30	97.8	98.1	98.4	98.6	99.1	99.5	99.6	100.2	101.6

Weight variation has shown almost similar to all the formulations as the total weight taken is 200 mg for the tablets. Friability percentage varies according to the concentrations of the PVP and F9 has shown the value of 0.38. Hardness is compared all

the formulations where F9 has shown the best result of 3 as it gives the optimum hardness which facilitates the disintegration of oral disintegration tablet. Thickness measured using vernier calipers which varies among all the formulations and optimized formulation is F9. Wetting time is calculated as per the IP for all the formulations and more time taken for the formulation F1 i.e. 57 sec as it implies to the disintegration and dissolution. Best result is obtained for the formulation F9 which has shown 15 sec which facilitates the disintegration. Assay is calculated for all the formulations F9 has shown the good result. The most important parameter which is evaluated for oral disintegration tablet is disintegration time which compared for all the formulations. Its ability to perform effectively as an ODT should be justified based on product performance. For such products, the extent of component solubility (e.g., tablet residue, need for liquids) can influence the acceptability of the product being labeled as an ODT. Disintegration time for ODT generally ranges from few sec to less than a minute. Here in the 9 formulations F1 has taken more time of 46 sec to disintegrate and F9 which is a optimized formulation disintegrated in 15 sec which clearly shown a very best result. Dissolution studies were carried out for all the formulations a s per IP and among all the formulations the results were 97.8, 98.1, 98.4, 98.6, 99.1, 99.5, 99.6, 99.8 and 100.2 in 30 sec for F1-F9 formulations respectively. In this F9 formulation which is composed of Crosscarmellose sodium as a superdisintegrant has shown the best release in 30 sec.

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