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Formulation and Evaluation of Taste Masked Orally Disitegrating Tablets of Diclofenac sodium

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Abstract: The purpose of this research was to mask the intensely bitter taste of diclofenac sodium and to formulate an orally-disintegrating tablet (ODT)) of the taste-masked drug. The methods commonly employed for achieving effective taste masking include various physical and chemical methods that prevent the drug substance from interaction with the taste buds. In this present study we have used veegum(magnesium aluminum silicate) as the taste masking agent and sodium starch glycolate and croscarmellose sodium as superdisintegrants.Granules of diclofenac sodium were prepared using different ratios of veegum (1:0.5, 1:1, 1:1.5, 1:2) by wet granulation method and evaluated for pre-compression parameters . With the help of *invitro* and *invivo* taste evaluation the optimum ratio (1:1.5) of the drug –veegum was determined. Fast dissolving tablets of diclofenac sodium were prepared using this ratio of drug – veegum and the superdisintegrants (2-5%) and evaluated for post compression parameters. Effect of superdisintegrants on wetting time, disintegrating time, fineness of dispersion, drug content, *in-vitro* release, have been studied. The results indicated that as the concentration of superdisintegrants increases disintegration time, dispersion time and *invitro* dissolution time decreases. Based on these tests the formulations containing 5% of sodium starch glycolate and croscarmellose sodium were selected as the optimum formulations. Short-term stability studies on promising formulations indicated that there were no significant changes .From this study, it can be concluded that taste masked diclofenac sodium fast disintegrating tablets can be successfully prepared using veegum as a taste masking agent (1:1.5) and the sodium starch glycolate and croscarmellose sodium (5%) as superdisintegrants.

Key words: Croscarmellose sodium, Diclofenac sodium, ODT, Super disintragrants, Sodium starch glycolate, Veegum.

Introduction

Orally disintegrating drug delivery systems (ODDS) are a new generation of formulations which combine the advantages of both liquid and conventional tablet formulations, and at the same time, offer added advantages over both the traditional dosage forms. Fast dispersible drug delivery system offer the luxury of much more accurate dosing than the primary alternative, This segment of formulation is especially designed for dysphagic, geriatric, paediatric and psychotic patients who are unable to swallow or refuse to swallow conventional oral formulations. They simply dispersed in the water, so cannot be hidden in mouth by psychotic patients.

The ODT has remarkable disintegration properties; it can rapidly disintegrate without water in the mouth within few seconds. When an ODT is placed in the

oral cavity, saliva quickly penetrates into the pores causing rapid disintegration. ODTs are also applicable when local action in the mouth is desirable such as local anesthetic for toothaches, oral ulcers, cold sores, or teething, and to deliver sustained release multiparticulate system to those who cannot swallow intact sustained action tablets/capsules.

Diclofenac sodium is a potent NSAID needed to get a faster action in any conditions which it have been used for. It is a drug with an intensely bitter taste; so if the taste of the drug is successfully masked and incorporated directly into an ODT, the main objective behind formulation of such a dosage form will definitely get futile. Thus in the present study an attempt has been made to mask the taste of diclofenac sodium and to formulate ODTs with good mouth feel so as to prepare a "patient-friendly dosage form.

Materials and Methods

Materials

Diclofenac sodium was a gift sample from Alembic Pharma, Veegum (Magnesium Aluminium Silicate) was a gift from Degussa India Private Ltd Mumbai, India. Sodium starch glycolate, Croscarmellose sodium, Mannitol, Microcrystalline cellulose was obtained from commercial sources. All other reagents were of analytical grade.

Preparation of taste masked granules

Drug and Magnesium aluminum silicate was mixed in different ratios (1:0.5, 1:1, 1:1.5, 1:2 separately) properly. And the mixtures were granulated using water till the end point was reached. The prepared granules were subjected to flow properties and evaluation of taste.

Preparation of orally disintegrating tablets:-

ODT tablets were prepared using super disintegrants addition. Different ratio of CCS and SSG were used (2-5%) [1-3]. The final formulae for preparation of ODT are given in the **Table No 1.** Accurately weighed taste masked granules of the optimized combination drug: Taste masking agent (1:1.5) were mixed with Croscarmellose sodium/ Sodium starch glycolate, MCC, Mannitol and saccharine for about 10-15 minutes. Then magnesium sterate and talc were added and mixed for further 10 minutes and compressed into tablets by direct compression method using Rotary type tablet punching machine.

Blend evaluation [4,-7]

Angle of repose, Carr's index, Bulk density, Tapped density and Hausner's Ratio were determined using conventional methods.

Taste evaluation of the granules

Evaluation of taste was done in two parts.

Determination of threshold bitterness concentration [8-9]

Various concentrations (1-30 mcg/ml) of pure drug were prepared in phosphate buffer pH 6.8. Mouth was rinsed with this solution and then, l0 ml of the most dilute solution was tasted by swirling it in the mouth mainly near the base of the tongue for 30 s. If the bitter sensation was no longer felt in the mouth after 30 s, the solution was spat out and wait for 1 min to ascertain whether this is due to delayed sensitivity. Then rinse with safe drinking water. The next highest concentration should not be tasted until at least 10 min have passed. The threshold bitter concentration was the lowest concentration at which a material continues to provoke a bitter sensation after 30 s. After the first series of tests, the mouth was rinsed thoroughly with safe drinking water until no bitter sensation remained. Minimum 6
volunteers were selected for this study.

Table 1: Composition of different formulations of taste masked ODT tablets

Formulation code	F1	F2	F3	F4	F5	F6
Granules (containing Diclofenac Sodium100mg)	250	250	250	250	250	250
Sodium starch Glycolate	10	15	25	-	-	-
Croscarmellose sodium	-	-	-	10	15	25
Mannitol	50	50	50	50	50	50
Saccharin	5	5	5	5	5	5
MCC	175	170	160	175	170	160
Magnesium stearate	5	5	5	5	5	5
Talc	5	5	5	5	5	5

***In vitro* evaluation of bitter taste of mixture**
An accurately weighed (5 mg drug equivalent) granules and 10 ml of pH 6.8 phosphate buffer (0.1 M) was taken in series of volumetric flask and stirred at 50 rpm. The stirring was stopped at different time intervals such as 0, 10, 30, 60, and 120 sec, and after completion of the respective intervals, dispersion was immediately filtered and the concentration of diclofenac sodium in filtrate was determined. Time for the mixture to achieve drug concentration corresponding to threshold bitterness in 10 ml phosphate buffer is recorded.

***In-vivo* evaluation of bitter taste of the mixture**
Taste evaluation was done using the time intensity method on 12 healthy human volunteers from whom informed consent was first obtained; mixture containing 5 mg diclofenac sodium was held in the mouth. Bitterness was recorded immediately and at several intervals for minutes according to the bitterness intensity scale from 0 to 3 where 0, 0.5, 1, 2, and 3 indicate no, threshold, slight, moderate, and strong bitterness.

Tablet evaluation

Diameter and thickness of the prepared tablets was determined using screw gauge.

Hardness and tensile strength of the tablets were determined by Monsanto tablet hardness tester.
Friability

Friability of the prepared ODT tablets was determined with the help of tablet friability apparatus at 25 rpm for 100 rotations. The pharmacopoeial limits of friability test for a tablet is not more than 1%.

Weight variation:
As per USP 20 tablets were weighed individually and average weight was calculated and maximum % deviation was found out. The tablets meet The USP test if not more than two tablets are outside the % Limit and if no tablets differs by more than two times the limit the weight variation tolerance for uncoated tablet depending on average tablet weight.

Drug content
Drug content was determined by dissolving tablet (500mg) of diclofenac ODTin 500 ml of 6.8 pH and analyzing 1ml of appropriately diluted sample at λ max 277 nm.

Wetting Time and Water Absorption Ratio
A double folded tissue paper was placed in a Petri dish. 6 milliliters of water containing a water-soluble dye (eosin) was added to the Petri dish. A tablet (preweighed) was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablet was noted as the wetting time. The wetted tablet was then weighed and the water absorption ratio, R, was determined using the equation,

$R = 100 (W_a - W_b)/W_b$

Where W_b and W_a are the weights of tablet before (dry weight) and after water absorption (wet weight), respectively.

Disintegration
The disintegration time of tablet was measured in water (37^0C) according to USP disintegration test apparatus. Three trials for each were performed.

Fineness of Dispersion
Fineness of the dispersion was done as an assessment of the grittiness which arises due to disintegration of the tablet into coarse particles. The test was performed by placing two tablets in 100 ml water and stirring it gently, till the tablets get completely disintegrated [10-11]. The formulation is considered to form a smooth dispersion if the complete dispersion passes through a sieve screen with a nominal mesh aperture of 710 μm without leaving any residue on the mesh.

***In Vivo* Disintegration Time, Sensory Evaluation of Roughness** [11-12]
In vivo disintegration was performed on 6 healthy human volunteers, from whom informed consent was first obtained. One tablet was held in the mouth after rinsing and the time required for complete disintegration of the tablet was recorded .The disintegrated material was held in the mouth for another 60 seconds, and then spat out. The mouth was rinsed with water without swallowing the disintegrated material and, finally, the roughness levels were recorded on a numerical scale ranging from 0 to 3 where 0, 1, 2, and 3 indicate no, slight, moderate, and high roughness, respectively.

***In vivo* Taste Evaluation** [11-14, 15]
Taste evaluation was done using the time intensity method on 12 healthy human volunteers from whom informed consent was first obtained. Tablet containing 500 mg diclofenac sodium was held in the mouth until complete disintegration. Bitterness was recorded immediately and at several intervals for 10 minutes according to the bitterness intensity scale from 0 to 3 where 0, 0.5, 1, 2, and 3 indicate no, threshold, slight, moderate, and strong bitterness.

Dissolution Studies
In vitro dissolution studies for all the fabricated tablets was carried out using USP paddle method at 100 rpm in 900 ml of phosphate buffer pH 6.8 as dissolution

media, maintained at 37±0.5°C. 5 ml aliquot was withdrawn at specified time intervals, filtered through whattman filter paper and assayed spectrophotometrically at 277nm. An equal volume of fresh medium, which was pre-warmed at 37°C, was replaced into the dissolution media after each sampling to maintain the constant volume throughout the test.

Statistical analysis

The difference in the release data for the different formulation was done by one way analysis of variance of means (ANOVA)at 5 % significance level using Microsoft 2007 excel package. Dissolution at 3 min was taken as the parameter for ANOVA analysis.

Stability studies

Stability studies were carried out on the promising formulations F3 and F6 only at 25^0 C/ 60% RH and 40 ^{0} C / 75% RH for 3 months. Different parameters like disintegration time, hardness, friability and dissolution rate were evaluated.

Table 2: Blend evaluation

Properties	Formulations (Granules)				
	1:0.5	1:1	1:1.5	1:2	Pure Drug
Angle of repose, degrees	22.16± 0.55	24.56±0.65	26.11±0.51	27.01± 0.44	20.32±0.67
Bulk density, g/cm^3	0.56± 0.29	0.49± 0.63	0.42± 0.25	0.40± 0.36	0.59±0.78
Tapped density g/cm^3	0.57± 0.35	0.54± 0.42	0.51± 0.28	0.48± 0.19	0.58±0.0.24
% Compressibility	7.48± 0.13	8.37± 0.17	9.82± 0.23	14.43± 0.30	7.01±0.45
Hausner ratio	1.01± 0.16	1.10± 0.17	1.21± 0.14	1.2± 0.14	1.01±0.24

Table 3: Determination of threshold bitterness concentration

Test	Concentrations in µg/ml						
	0 sec	10 sec	30sec	60sec	120sec	180 sec	240 sec
In vitro evaluation of bitterness (1:1.5)	0	1.78	5.6	8.2	11.42	13.46	15.18
Bitterness threshold concentration	20µg/ml						

Table 4 : *In vitro* and *In vivo* evaluation of taste of the prepared granules

Granules :Veegum	In-vitro taste evaluation	In-vivo		
		0 min	30 sec	1min
Diclofenac sodium alone	<1 min	3	3	3
1:0.5	< I min	2	3	3
1:1	<2 min	0	1	2
1:1.5	>4 min	0	0	0
1:2	>4 min	0	0	0

Fig 1: Comparison of the wetting time and disintegration time

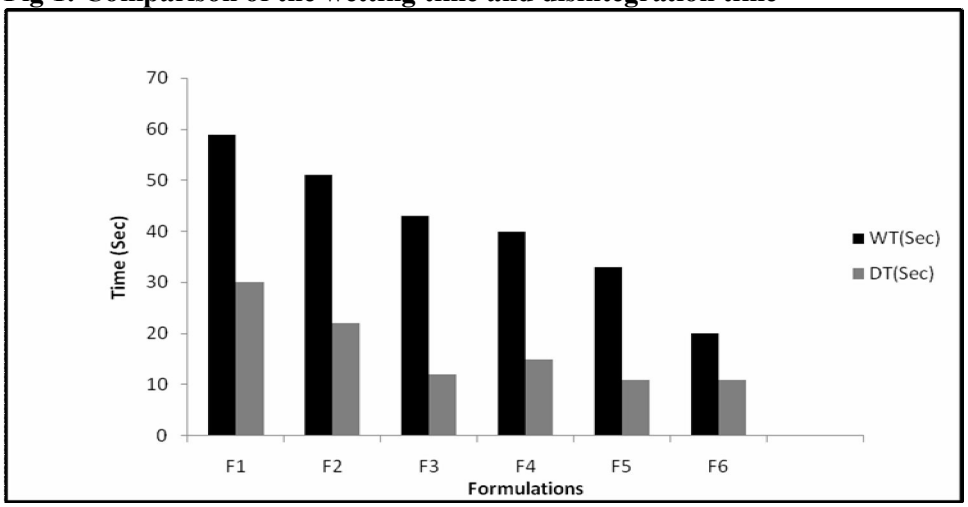


Fig 2: Comparison of the *in vitro* and i*n vivo* disintegration time

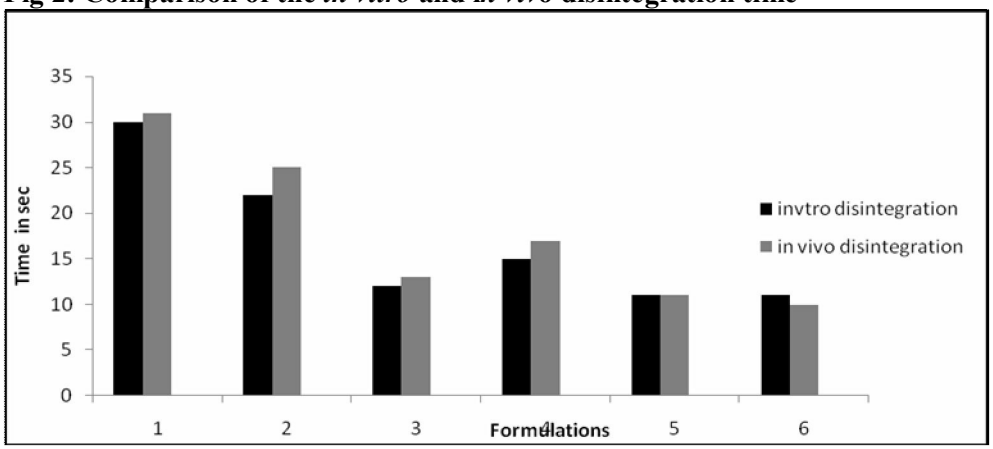


Table 5: Evaluation of the ODT tablet formulations

Tests	Formulations					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Diameter (mm)	8.00±0.02	8.1±0.05	8.0±0.08	7.9±0.05	8.0±0.08	8.3±0.08
Thickness (mm)	3.53±0.02	3.56±0.1	3.50±0.01	3.49±0.01	3.53±0.01	3.51±0.03
Hardness (kg/cm^2)	3.0±0.009	3.2±0.1	3.15±0.5	3.3±0.3	2.9±0.5	3.2.±0.8
Weight variation	0.42	0.53	0.45	0.40	0.55	0.49
Friability (%)	0.75±0.09	0.78 ±0.5	0.76 ± 0.3	0.69 ±0.6	0.71 ± 0.7	0.73±0.8
Drug Content (%)	99 ±1.5	100±0.98	98 ±1.2	99±0.75	100±2.46	99±1.8
Wetting time (sec)	58.8 ±1.2	51.1±5.3	43±0.8	40±1.5	33±2.1	20±1.7
Water Absorption ratio	129±2.1	137±6.8	154±2.7	118±1.31	123±1.2	125±5.4
Disintegration (Sec)	30±2.3	22±5.4	12±2.4	15±4.9	11±1.6	8±3.8
Fineness of dispersion	Pass	Pass	Pass	Pass	Pass	Pass

Table 6 : *in vivo* evaluation of disintegration ,Roughness and Taste

Test	Formulations					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
In vivo disintegration	31	25	13	17	11	10
Sensory evaluation of roughness	0	0	0	0	0	0
In-vivo taste evaluation (up to 10 min)	0	0	0	0	0	0

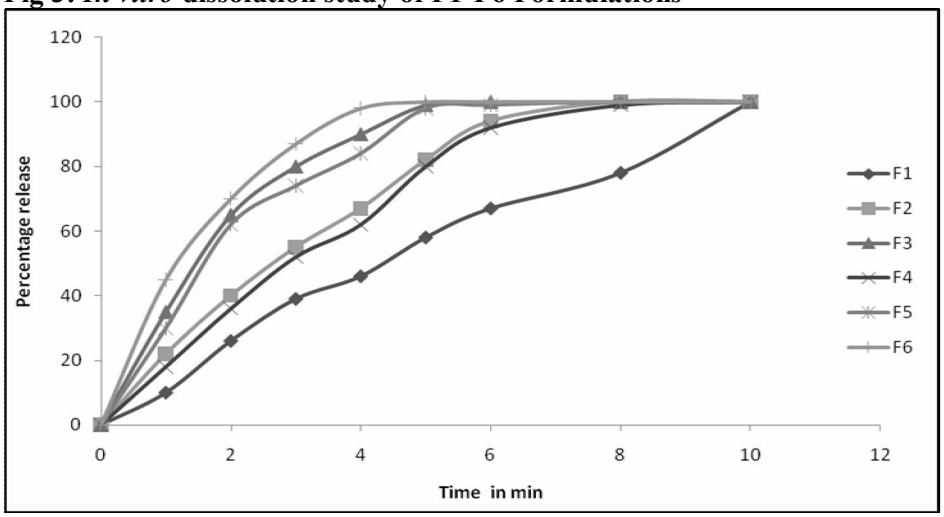
Table 7: Statistical analysis (One way ANOVA)

ANOVA						
Source of Variation	SS	df	MS	F	P –Value	F Crit
Between Groups	8967.11111	5	1793.42	13.6729	0.00013	3.10588
Within Groups	1574	12	131.167			
Total	10541.11111	17				

Table 8: Stability study of the optimized formulations F3 and F6

Test	Formulations	25^{O} C/ 60% RH				40^{O} C / 75% RH			
		Time period in months				Time period in months			
		0	1	2	3	0	1	2	3
Content uniformity	F3	99.16	99.34	99.67	99.13	99.45	99.65	99.67	99.19
	F6	99.75	99.67	99.12	99.76	99.90	99.17	99.56	99.78
Disintegration	F3	12.8	11.7	12.0	12.2	11.5	11.9	12.3	12.1
	F6	8.1	8.6	7.9	8.0	7.8	8.2	8.5	7.9
Friability	F3	0.75	0.76	0.74	0.75	0.73	0.75	0.76	0.74
	F6	0.74	0.76	0.75	0.74	0.75	0.74	0.73	0.75
Hardness	F3	3.2	3.16	3.18	3.22	3.1	3.16	3.14	3.08
	F6	3.22	3.18	3.24	3.20	3.24	3.22	3.20	3.22

Fig 3: *In vitro* dissolution study of F1-F6 Formulations



Result and Discussion

The present study was carried out to prepare taste masked diclofenac sodium orally disintegrating tablets that can be used for the successful management of pain and inflammation. The bitter taste of diclofenac sodium was masked by using veegum. The taste masked granules were prepared by wet granulation method. Mouth disintegrating tablets were prepared using super disintegrants like sodium starch glycolate, croscarmellose sodium. Six formulations (F1 - F6) were prepared by using Superdisintegrants in a concentration ranging from 2-5% Table No -1.

The preformulation studies conducted on the prepared granules containing different ratio of veegum like angle of repose, Carr's index, bulk density showed good flow property and compressibility Table No -2. The threshold concentration of diclofenac was determined as 20µg/ml and in vitro taste masking study on the prepared granules revealed that the granules prepared 1:0.5 and 1:1 are failed to mask the taste (<2 min).an in vivo taste evaluation was also done on the granules for finding out the optimum ratio of diclofenac sodium – veegum mixture .From that study we concluded that granules prepared with veegum in the ratio of 1:1.5 can be taken as an optimum ratio the for successful taste masking (Table - 3 and 4) .No bitter taste was experienced > 5min for this combination and the concentration was found to be 15.18 µg/ml up to 4 min which was fairly below the threshold concentration(Table-3and 4) .So all formulations (F1-F6) prepared using the granules prepared by taking the diclofenac sodium : veegum in the ration of 1:1.5 and in the formulation F1- F3 super disintegrants sodium starch glycolate was added in a concentration ranges from 2 -5% . The formulations F4- F6 were prepared with croscarmellose sodium as super disintegrants in a concentration ranges from 2-5%. The prepared tablets in all formulations possessed good mechanical strength with sufficient hardness and the values obtained lies between 3.0- 3.3kg/cm^2. Percent friability were less than1% in the all formulations and the values obtained lies between 0.69-0.78%.All the tablets from each formulation passed weight variation test, as the percentage weight variation was within the pharmacopoeial limits. The thickness was almost uniform in all formulations and the values obtained were between 3.49 – 3.56 mm.

The tablets were evaluated for the *in vitro* disintegration time and it was observed that the time for all the formulations varied from 8±3.8 - 30±2.3s It was found that as the concentration of sodium starch glycolate and croscarmellose sodium increase the disintegration time decreases. It was noted that the disintegration time of the tablets prepared with croscarmellose sodium at lower level (10mg) is almost same that of the higher level of (25mg) of the starch glycolate .The disintegration time of the F3 and F6 are found to be lowest among the formulations. An in-vivo disintegration test using human volunteers was also performed and compared with the in-vitro disintegration test. There was an excellent correlation between *invitro* and *invivo* disintegration time in all the formulation. The formulation F3 and F6 showed faster *invitro* and *invivo* disintergration.Results were shown in table -05, 6 and Figure-1.

Because the dissolution process of a tablet depends on the wetting followed by disintegration of the tablet, the measurement of wetting time may be used as another confirmative test for evaluation of the fast dissolving tablets. In the wetting time study, the wetting time was rapid in formulations containing CCS than SSG. It was observed that as the concentrations of CCS, SSG increased, the time taken for wetting was reduced. Result was shown in table -05.The comparison of the disintegration time and wetting time for F1–F6 formulations were shown in Figure-2.

For the better patient compatibility Oral disintegrating tablets should produce a fine dispersion during disintegration. All the formulations passed the *Invitro* and *invivo* test for fineness of dispersion indicate that the concentration of super disintegrants selected were able to produce a fine dispersion during disintegration.

The time intensity study for taste in human volunteers of both the Diclofenac veegum mixture and ODT revealed considerable masking of the bitter taste of diclofenac sodium up to 10 min with degree of bitterness below the threshold value (20µg/ml). Sensory evaluation of all the formulation containing the optimized diclofenac veegum granules proved good palatability. Table- 6.

In vitro dissolution studies for all the fabricated tablets were carried out using USP paddle method at 100 rpm in 900 ml of phosphate buffer pH 6.8 as dissolution media. Formulations F1 shows 80 % of the drug release at < 10 min. F2 ,F3 showed 80% release with in 5 min and 3min.respectively.As the concentration of the starch glycolate increased from 2% -5% there was a remarkable decrese in the dissolution time. Formulation F4-F6 showed its 80% release at 5 min, 4min and less than 4 min respectively.Formulations F4-F6 showed greater reduction in dissolution time as the concentration of cross caremellose sodium increased. The Figure-3 shows the comparative dissolution profile of 6 batches of formulations. The rapid increase in dissolution of diclofenac with the increase in CCS may be attributed to rapid swelling and disintegration of the tablet into apparently primary particles. Tablets prepared with SSG disintegrate by rapid uptake of water followed by rapid and enormous swelling into primary particle, but more slowly.

The differences in the release of the formulations were done by one way analysis of variance of means

(ANOVA) at 5 % significance level using Microsoft 2007 excel package. Dissolution at 3 min was taken as the parameter for ANOVA analysis. All the formulations were found to be significantly different ($p < 0.001$).Result was shown in Table-7.

From all the evaluation study the formulation F3 and F6 were considered as optimum formulations which showed lesser disintegration time, wetting time, dissolution time.

These optimum formulations were taken for further stability studies. Stability studies were carried out at 25^{O} C/ 60% RH and 40^{O} C / 75% RH for 3 months. Different parameters like, drug content, disintegration time, hardness, and friability were evaluated. By observing the effect of storage and temperature on disintegration time, rate of dissolution, friability and hardness, it was confirmed that the formulated tablets F3 and F6 posses good stability. Stability study results confirm that all parameters of prepared formulation remain unchanged. Both the formulations showed no significant variations in all the parameters and were found to be stable. Results are given in Table-8.

Conclusion

It was concluded that the methods used for taste masking of bitter drug diclofenac sodium were found to be effective and orally dissolving tablets of the same pass all the pharmacopoeial standards.

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