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FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF TRAMADOL HYDROCHLORIDE

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Abstract:

Attempts have made for the development of fast disintegrating tablets of Tramadol hydrochloride by direct compression and wet granulation methods. Tramadol ((±)-*trans*-2-(dimethylaminomethyl)-1-(*m*-methoxyphenyl)-cyclohexanol) is an orally active synthetic opioid agonist analgesic. Its mechanism of action derives from its attachment to the μ- receptor and blockage of norepinephrine and serotonin reuptake. It's reported adverse effects include nausea, dizziness, and sleepiness, dry mouth, sweating and lowering of seizure threshold. Tramadol hydrochloride shows a good efficacy and safety profile and controls the pain symptoms. The drug and excipients were examined for the pre-compression parameters. The prepared formulations were evaluated for hardness, weight variation, friability, dispersion time, water absorption ratio, disintegration, dissolution and stability studies. The values of pre-compression parameters were within prescribed I.P. limits and indicate good free flowing properties. In all the formulations friability was less than 1% indicates tablets had a good mechanical resistance. Hardness of the tablets was found to be in the range of 40.6 to 47.5N.The disintegration of all formulation were decreased with increase in the concentration of disintegrating agents like crosspovidone, copovidone and also with Pharmaburst. The tablet formulation prepared with Pharmaburst (F13) showed good flow properties, low disintegration time (15 s) and improved drug release (99 % at 30 min) compared with those of the reference product (88 % at 30 min) and passes 6 months accelerated stability testing's.

Keywords: Mouth dissolving tablets, Tramadol hydrochloride, direct compression method, wet granulation method, pain, crosspovidone, copovidone.

Introduction

The oral route is the most preferred route for administration of therapeutic agents because of ease of administration, accurate dose, self medication and patient compliance. In this regard, tablets and capsules are most preferred dosage forms for oral route. But these dosage forms are difficult to administer to children and geriatrics. Hence, MDT are favoured for its ease of administration and improvement in therapeutic efficacy of dosage form [1-3].

Mouth dissolving tablets (MDT) disintegrate and/or dissolve in the mouth (in saliva) within a few seconds without any need to administer it with liquid. They are also called fast dissolving, oro-dispersible, orally disintegrating and fast melting tablets. MDT combines the advantages of both conventional and liquid formulations [4,5].

Tramadol HCl is a central acting analgesic used in management of chronic pain. Tramadol HCl is clinically effective in the treatment of moderate to severe pain with a relative low addiction incidence. Tramadol produces analgesia against multiple acute and chronic pain conditions, such as post surgical pain, obstetric pain, terminal cancer pain and pain of coronary origin, and it has been used as adjuvant therapy in anesthesia. The drug is available as a conventional tablet, so there is need to develop the mouth dissolving tablets to allow the administration of dosage form with out need of water which is particularly important for pediatrics and geriatrics. Tramadol hydrochloride Oral dispersible tablets are currently available in USA and Europe and there is no marketed product in India. Therefore, the present work focused on mouth dissolving tablets due to the increasing proportion of the aged in the population and also because of the need to develop appropriate dosage form for the elderly.

Materials and Methods

Materials

Tramadol hydrochloride was received as a gift from jubilant life sciences, Noida and other excipients used in this work was obtained as gifts from BASF, India.

Preparation of mouth dissolving tablets

Initially, four batches of tramadol HCl mouth dissolving tablets were formulated by direct compression method and four additional batches were formulated by wet granulation method with the same composition as that of the reference product (Rybix ODT, Shionogi Inc, USA).

Tramadol hydrochloride, mannitol, crospovidone, copovidone, ethyl cellulose and pharmaburst were individually sifted through # 40 mesh and neotame, tutti frutti flavor, silicon dioxide, colloidal anhydrous silica and magnesium stearate was sifted through # 60 mesh and collected separately in a polyethylene bag.

Tramadol hydrochloride, mannitol, crospovidone, copovidone, and ethyl cellulose were placed in a blender and mixed thoroughly for 10 min; sifted silicon dioxide and magnesium stearate were added to the blend and mixed for 5 min. The final blend was compressed into tablets by using a rotary compression machine.

Wet granulation method was used with water as granulating fluid. Initially, the active ingredient and mannitol were dry-mixed and added to the binder solution (water and crospovidone) to obtain a wet mass. dried and blended with crospovidone and ethylene cellulose in blender for 10 min. The sifted silicon dioxide and magnesium stearate were added and mixed for 5 minutes in blender. The lubricated blend was compressed into tablets by using rotary compression machine.

Evaluation of blend parameters

Procedure for Bulk density and Tapped density:

50 grams of powder blend was taken and poured into 100ml measuring cylinder, then noted down the initial volume of powder and calculated the bulk density. Then immediately started the tapings of powder, the powder was allowed to fall under its own weight and after completion of tapings noted down the tapped volume and calculated the tapped density of powder. The tapping was continued until no further change in volume was noted.[6, 7]

Compressibility index/Carr's index:

Compressibility index is the most important parameter to measure the flow ability of powder obtained from the bulk and tapped densities. According to theoretical concern, less the compressibility index of blend, it is more flow able. The Carr's index value of blend is less than 15 then it's defined as free flowing material.

Evaluation of Mouth dissolving tablets of Tramadol HCl:

General Appearance:

The general appearance, general elegance and identity of tablet are essential for consumer acceptance, for control and maintenance of batch-to-batch uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, color, break line, debossing, presence or absence of odor, taste etc.

Hardness:

Tablet requires a certain amount of hardness and strength to withstand mechanical shakes during manufacture, packaging and transportation. Hence, hardness generally measures the tablet crushing strength.

Friability:

Tablets friability can be determined by Roche Friabilator. This consists of a plastic chamber that revolves at 25 rpm; nearer to 6.5 grams of tablets were dropped from six inches height through a head space of the plastic chamber. Then Friabilator was operated for 100 revolutions and then tablets are reweighed. The tablets loose less than 1.0% of its original weight are considered as acceptable.[8]

Weight Variation test:

Twenty tablets were taken randomly, weighed individually and calculated average weight of twenty tablets and compare the individual tablet weight with average tablet weight. The tablet passes the Ph.Eur test of uniformity of weight limits if not more than 2 of the individual masses deviate from the average weight by more than the percentage deviation and none deviates by more than twice that percentage.[9]

Disintegration test:

Disintegration test is conducted to determine whether the tablets disintegrate with in the prescribed time when placed in the medium under experimental conditions.

Dispersion time:

A tablet was placed in a petridish containing 10 ml of pH 7.4 phosphate buffer (saliva pH media) and time to disperse the tablet completely was noted down.

Water absorption ratio:

A twice folded tissue paper was placed in a petridish containing 5 ml of water and the tablet was carefully placed on the paper and allowed to wet completely. Then reweighed the wetted tablet and calculated the water absorption ratio.

Stability studies:

According to ICH guidelines the optimized formulation i.e. TM 13 trail was packed in Alu–Alu blisters and charged for stability at accelerated conditions 40°C/75% RH for studying stability of the drug product during its shelf-life. Tablets

were withdrawn from stability chambers at 1st, 2nd, 3rd & 6th month and analyzed for assay, dissolution, friability, disintegration and dispersion time.[10]

Results and Discussion

Tramadol HCl is a right and suitable candidate for preparation of mouth dissolving tablets. In this study the tablets were prepared with the aim to minimize the disintegration time, improve the drug release rate and to mask the bitter taste of the drug. The trails were formulated with Pharmaburst as excipients to optimize the disintegration time and drug release rate. The unpleasant taste was masked by using neotame as sweetener and tutti frutti as flavor.

Table-01: Formulation trails of Tramadol HCl by direct compression.

Composition	Unit formula (mg/tablet)			
	TM 01	**TM 02**	**TM 03**	**TM 04**
Tramadol HCl	50	50	50	50
Mannitol	88.75	84.25	81.25	78.25
Crospovidone	3.0	4.5	6.0	7.5
Copovidone	3.0	3.75	3.75	3.75
Ethyl cellulose	1.5	1.5	1.5	1.5
Silicon dioxide	0.75	1.5	1.5	1.5
Magnesium stearate	3.0	4.5	6.0	7.5
Total tablet weight	**150.0**	**150.0**	**150.0**	**150.0**

Table-02: Formulation trails of Tramadol HCl by wet granulation.

Composition	Unit formula (mg/tablet)			
	TM 05	**TM 06**	**TM 07**	**TM 08**
Tramadol HCl	50	50	50	50
Mannitol	88.75	84.25	81.25	78.25
Crospovidone	3.0	4.5	6.0	7.5
Copovidone	3.0	3.75	3.75	3.75
water	q.s.	q.s.	q.s.	q.s.
Ethyl cellulose	1.5	1.5	1.5	1.5
Silicon dioxide	0.75	1.5	1.5	1.5
Magnesium stearate	3.0	4.5	6.0	7.5
Total tablet weight	**150.0**	**150.0**	**150.0**	**150.0**

Table-03: Formulation trails of tramadol HCl with pharmaburst.

Composition	Unit formula (mg/tablet)		
	TM 09	**TM 10**	**TM 11**
Tramadol Hydrochloride	50	50	50
Pharmaburst	97	95.5	94
Colloidal anhydrous silica	---	---	1.5
Magnesium stearate	3.0	4.5	4.5

Total tablet weight	**150.0**	**150.0**	**150.0**

Table-04: Formulation trails with sweetener and flavor.

Composition	**Unit formula (mg/tablet)**	
	TM 12	**TM 13**
Tramadol Hydrochloride	50	50
Pharmaburst	92.35	91.45
Neotame	**1.5**	**2.25**
Tutti frutti flavor	**0.15**	**0.3**
Colloidal anhydrous silica	1.5	1.5
Magnesium stearate	4.5	4.5
Total tablet weight	**150.0**	**150.0**

Drug excipients compatibility studies

Compatibility studies by Physical observation

After completion of the one month period the results revealed that there was no noticeable change in any physical mixture and the observations of the mixtures were given in table 05.

Table-05: Drug and excipients compatibility studies by Physical Observation.

Drug + Excipient	**Initial Appearance**	**Observation**	
		40ºC/75% RH	**50ºC/75% RH**
Drug (Tramadol HCl)	White coloured powder	NCC	NCC
Drug + Mannitol	White to off-white Powder	NCC	NCC
Drug + Crospovidone	White to off-white Powder	NCC	NCC
Drug + Copovidone	White to off-white Powder	NCC	NCC
Drug + Ethyl cellulose	White to off-white Powder	NCC	NCC
Drug + Silicon dioxide	White to off-white Powder	NCC	NCC
Drug + mint flavor	White to off-white Powder	NCC	NCC
Drug + aspartame	White to off-white Powder	NCC	NCC
Drug + Pharmaburst	White to off-white Powder	NCC	NCC
Drug + Neotame	White to off-white Powder	NCC	NCC
Drug + Tutti frutti	White to off-white Powder	NCC	NCC
Drug + Colloidal anhydrous silica	White to off-white Powder	NCC	NCC
Drug + Mg. stearate	White to off-white Powder	NCC	NCC
Physical mixture	White to off-white Powder	NCC	NCC

NCC: No Colour Change

Compatibility studies by FTIR studies:

The FTIR studies were conducted for completed physical mixture and drug substance. The completed physical mixture was evaluated against drug substance and the graphs of the same were shown in figure 01 - 02.

After completion of the study the IR spectrums were generated and spectrums of both active substance alone and physical mixture revealed that the bands observed in the active substance were appeared in the physical mixture. This means that confirming the purity of active substance with standard respectively and interpretation data were given in table 06.

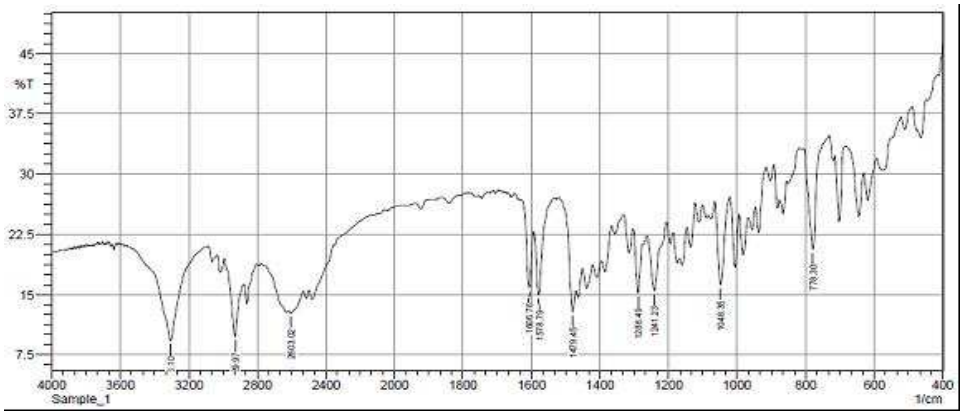

Figure 01: FTIR Spectra of Tramadol HCl drug substance.

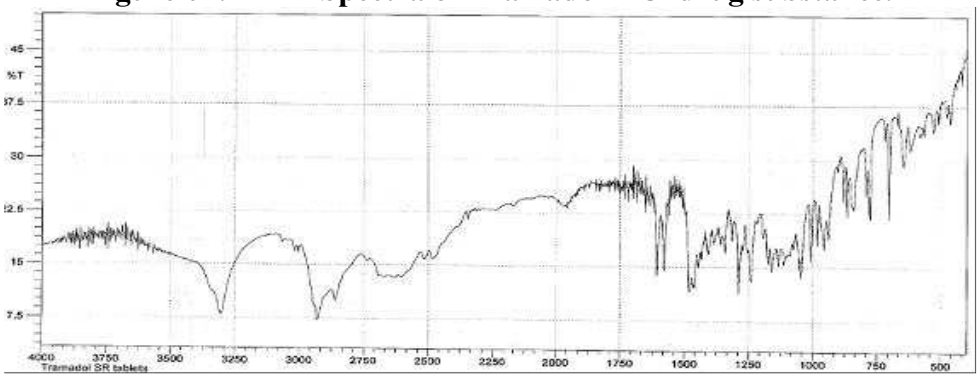

Figure 02: FTIR Spectra of Tramadol HCl tablets.

Table-06: Interpretation data for Tramadol HCl mouth dissolving tablets.

Figure No	Name of the Compound	Functional Group Assigned (wave number in cm^{-1})					
		C-Hstr aromatic	C=C	-C-H ben	=C-Hstr	C-O str	C-Nstr
-	Characteristic peak	3000-3100	1400-1600	1350-1480	2720-2850	1000-1300	1030-1230
01	Drug (Tramadol HCl API)	3051.44	1578.79	1479.45	2860.53	1241.23	1048.35
02	Tramadol HCl Tablets	3051.15	1578.23	1477.65	2856.15	1239.19	1051.56

Wavelength of Tramadol hydrochloride

Based on UV-data it was concluded that the drug was shown a maximum absorbance at 215nm in both 0.1N HCl and pH 7.4 phosphate buffers (saliva pH). So, 215nm was selected as maximum wavelength for further experimental trials.

Placebo interference

The excipients interference was studied at selected wavelength in 0.1N HCl and pH 7.4 phosphate buffers. From the data it was observed that each excipients absorbance in both medias is below 0.03% and the physical mixture of excipients showed below 0.06% at the selected wave length region and confirms that there is no interference for the selected excipients and the results of the same were given in table 07.

Table-07: Absorbance of excipients at 215 nm.

Medias →	**0.1N HCl**	**pH 7.4 phosphate buffer**
Excipients ↓	**Absorbance at 215 nm (n=3) in %**	
Mannitol	0.030	0.024
Crospovidone	0.021	0.019
Copovidone	0.017	0.019
Ethyl cellulose	0.014	0.016
Silicon dioxide	0.009	0.011
Pharmaburst	0.016	0.018
Colloidal anhydrous silica	0.010	0.012
Aspartame	0.09	0.08
Mint flavor	0.08	0.08
Neotame	0.012	0.011
Tutti frutti flavor	0.006	0.006
Magnesium stearate	0.009	0.010
Physical mixture	0.058	0.059

Standard graph of Tramadol HCl by UV method

The different concentrations of standard solution was prepared and measured the absorbance at 215nm in both medias i.e. 0.1N HCl and pH 7.4 phosphate buffer. The standard curve parameters were given in table 08. The absorbance in both medias was given in table 09- 10 and the graph of concentration Vs absorbance was plotted and shown in figure 03 - 04. The results showed that the detector response was found linear with a correlation coefficient of 0.9991 and 0.9994 in both medias i.e. 0.1N HCl and pH 7.4 phosphate buffer respectively and this was utilized for further estimation of drug content in dissolution studies from the mouth dissolving tablets.

Table 09: Absorbance of Tramadol HCl at 215nm in 0.1N HCl.

Concentration (µg/ml)	Absorbance at 215nm
0	0
5.55	0.19
13.88	0.37
27.78	0.71
41.66	1.06
55.55	1.39
83.33	2.03
111.1	2.64

Table-10: Absorbance of Tramadol HCl at 215nm in pH 7.4 phosphate buffer.

Concentration (µg/ml)	Absorbance at 215nm
0	0
5.55	0.15
13.88	0.34
27.78	0.65
41.66	0.95
55.55	1.24
83.33	1.9
111.1	2.45

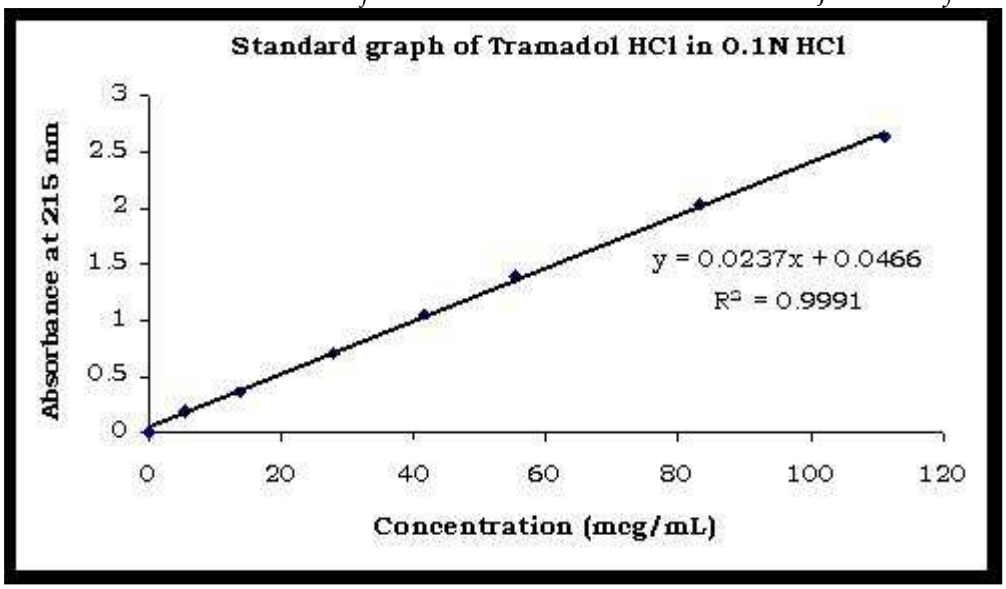

Figure 03: Standard graph of Tramadol HCl in 0.1N HCl.

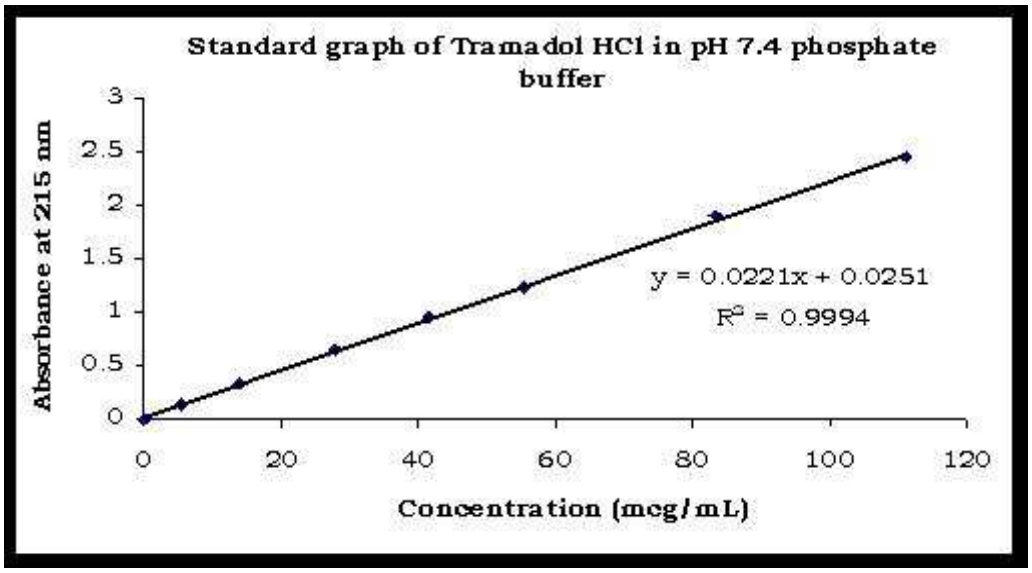

Figure 04: Standard graph of Tramadol HCl in pH 7.4 phosphate buffer.

Evaluation of Tramadol HCl mouth dissolving tablets.

Blend Evaluation:

Initially the trails TM 01-TM 04 was formulated with direct compression method. The trails TM 01 & TM 02 blends showed very poor flow properties and the trails TM 03 & TM 04 blends showed poor flow properties even though the concentration of lubricant increases to higher limit as defined in the hand book of pharmaceutical excipients.

Next four more trails i.e. TM 05-TM 08 was formulated with wet granulation technique. The trails TM 05 & TM 06 blends showed very poor flow properties and the trails TM 07 & TM 08 blends showed fair flow properties and the flow of blend were not improved even though the method of preparation changed.

Next three more trails i.e. TM 09-TM 11 was formulated with direct compression method by changing the composition and the trails TM 09 & TM 10 blends showed good flow properties and TM 11 trail showed very good free flow of blend.

Further two more trails i.e. TM 12-TM 13 were planned for optimization of sweetener and flavor and both trails showed very good free flow of blend and the results of all trails were given in table 11.

Table 11: Evaluation of blend for all trails TM 01-TM 13.

Batch No	Bulk density(gm/cc)	Tapped density (gm/cc)	Compressibility Index (%)
TM 01	0.66	1.00	34
TM 02	0.68	1.02	33
TM 03	0.66	0.90	27
TM 04	0.66	0.89	26
TM 05	0.71	0.95	25
TM 06	0.72	0.94	23
TM 07	0.74	0.93	20
TM 08	0.74	0.92	20
TM 09	0.72	0.88	18
TM 10	0.72	0.86	17
TM 11	0.70	0.80	13
TM 12	0.70	0.78	10
TM 13	0.70	0.78	10

Evaluation of parameters for mouth dissolving tablets:

All trails of tablets were evaluated for various parameters such as Appearance, Hardness, Friability, Weight variation, Disintegration test, Dispersion time and Water absorption ratio.

Appearance: All trails of tablets showed very good appearance without any capping or lamination and found satisfactory.

Hardness: The hardness of tablets was tested by Monsanto hardness tester and the result varies from 40-50 N. The hardness of all trials of tablets was found satisfactory and results were given in table 12.

Table-12: Evaluation parameters for all trials of tablets.

Batch No	Hardness (N)	Friability (%)	Weight variation(mg)	Disintegration time (Sec)
TM 01	45 ± 0.7	0.11 ± 0.03	148.2 ± 1.15	104 ± 1.85
TM 02	44 ± 0.9	0.12 ± 0.02	147.9 ± 1.64	95 ± 2.12
TM 03	41 ± 0.6	0.11 ± 0.04	150.5 ± 1.86	84 ± 2.15
TM 04	42 ± 1.4	0.13 ±0.06	149.1 ± 1.22	78 ± 2.52
TM 05	47 ± 0.5	0.10 ± 0.05	148.6 ± 1.26	98 ± 1.85
TM 06	42 ± 1.1	0.11 ± 0.02	146.2 ± 2.24	87 ± 1.26
TM 07	40 ± 0.8	0.12 ± 0.05	148.5 ± 1.95	75 ± 1.65
TM 08	41 ± 0.7	0.16 ± 0.03	148.2 ± 2.16	60 ± 1.18
TM 09	40 ± 0.6	0.10 ± 0.08	147.3 ± 2.12	45 ± 1.24
TM 10	43 ± 0.8	0.13 ± 0.09	148.2 ± 1.24	28 ± 1.02
TM 11	41 ± 0.8	0.12 ± 0.06	147.9 ± 1.28	15 ± 0.68
TM 12	42 ± 0.9	0.11 ± 0.06	148.5 ± 1.08	16 ± 0.89
TM 13	41 ± 0.8	0.12 ± 0.08	148.6 ± 1.15	15 ± 0.62

Data presented as Mean ± SD

Friability

Tablet strength was tested by Roche Friabilator and the tablets of all trials showed very good friability with less than 0.2% which is well within wide accepted range of Pharmacopoeias limit (1.0%) and results were given in table 12.

Weight Variation

The average weight of all tablets were found acceptable limit of within 5% for all the trails and results were given in table 12.

Disintegration test

Disintegration test was conducted for all trails and found within the limits of Pharmacopoeial standards i.e. less than 3 minutes. But as per our concern target result is less than 1 minute. The trails TM 01-TM 08 not meeting the target result and the trails TM 09-TM 13 meeting the target disintegration time and the results of the same were given in table12.

Dispersion time

The dispersion time was conducted for optimized formulation TM 13 and observed dispersion time was given in table 13 and the figure of the same was shown in figure 05-06.

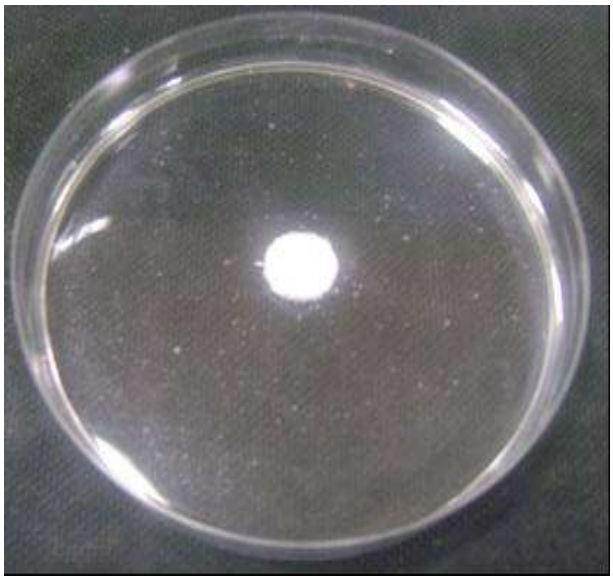

Fig 05 Dispersion time of tablet at 6 secs

Fig 06 Complete dispersion of tablet at 16 secs

Water absorption ratio

The water absorption ratio was performed to assess how much amount of water absorbed by the tablet by subtracting the weight of the tablet before absorption from the weight of tablet after absorption. The water absorption ratio was performed for optimized formulation (TM 13) and the result was given in table 13.

Table-13: Results of dispersion time and water absorption ratio.

Parameter	TM 13
Dispersion time (Sec)	10 ± 0.24
Water absorption ratio (%)	103.2 ± 0.62

Data presented as Mean ± SD

Evaluation of *In-vitro* drug release studies

Initially the formulation trails were started with same composition as that of reference product and the trails i.e. TM 01-TM 04 was prepared with direct compression technique. In case of dissolution, the trails TM 01-TM 04 showed slow and extent of drug release and not matching the reference product drug release. The results of the drug release were given in table 14 and the graph of the same was showed in figure 07.

Table-14: *In-vitro* dissolution data for trails TM 01-TM 04 Vs Reference product.

Time in minutes	Reference product	% Cumulative Drug Release (%RSD)			
		TM 01	TM 02	TM 03	TM 04
05	82 ± 1.84	49 ± 1.54	53 ± 1.52	59 ± 1.41	68 ± 1.24
10	87 ± 1.23	64 ± 1.63	69 ± 1.06	68 ± 1.06	76 ± 1.19
15	93 ± 1.08	72 ± 1.52	75 ± 2.12	73 ± 1.42	81 ± 1.38
30	96 ± 1.24	79 ± 2.36	80 ± 1.57	80 ± 1.61	86 ± 1.64

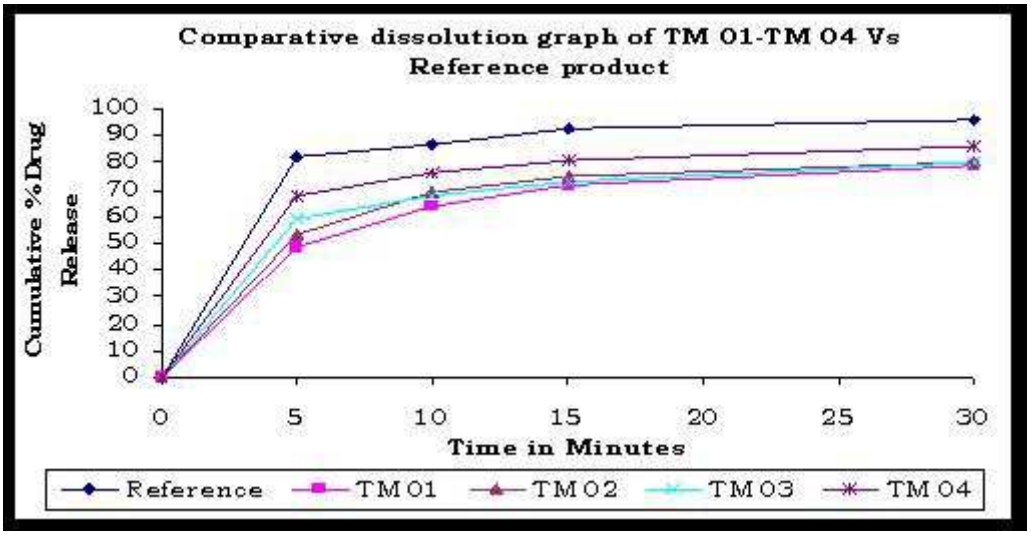

Figure 07: Comparative dissolution graph of TM 01-TM 04 Vs Reference product.

The trails TM 05-TM 08 was prepared by wet granulation technique using same composition as TM 01-TM 04. In case of dissolution, the tablets showing similar drug release as TM 01-TM 04 and no improvement was observed in drug release at all time points and not meeting with reference product drug release. The results of the drug release were given in table 15 and the graph of the same was showed in figure 08.

Table-15: *In-vitro* dissolution data for trails TM 05-TM 08 Vs Reference product.

Time in minutes	Reference product	% Cumulative Drug Release (%RSD)			
		TM 05	TM 06	TM 07	TM 08
05	82 ± 1.84	52 ± 1.26	54 ± 1.09	58 ± 1.23	66 ± 1.64
10	87 ± 1.23	68 ± 1.32	68 ± 1.18	70 ± 1.62	78 ± 0.89
15	93 ± 1.08	72 ± 1.05	78 ± 1.58	79 ± 0.68	83 ± 1.29
30	96 ± 1.24	81 ± 1.62	84 ± 0.95	85 ± 1.05	89 ± 1.03

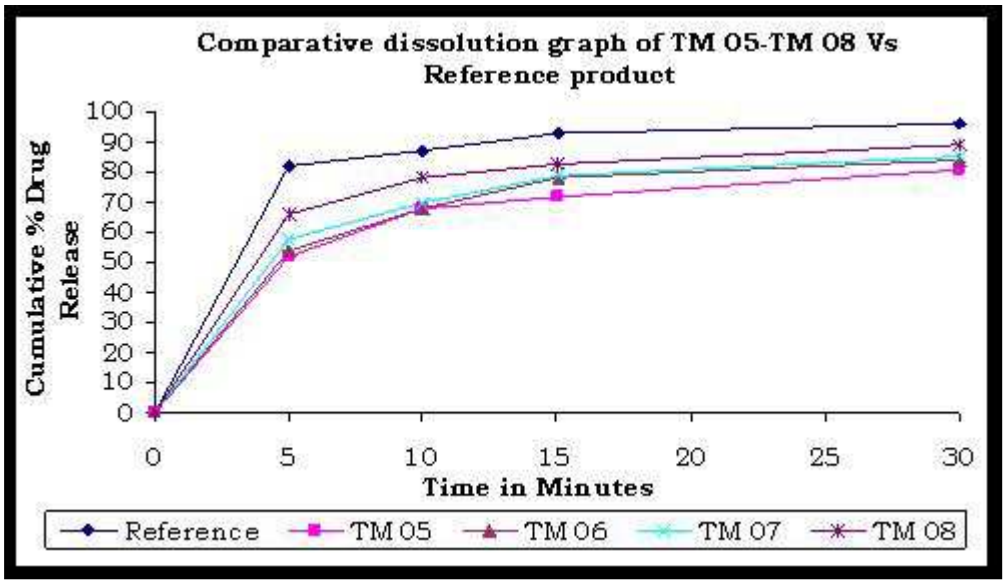

Figure 08: Comparative dissolution graph of TM 05-TM 08 Vs Reference product.

Due to poor flow of blend and deviation in drug release studies, next three more trails i.e. TM 09-TM 11 was planned with different composition. The trail TM 09 showed better drug release than previous trails, but need to improve the flow of blend. The trail TM 10 showed good release than TM 09, but slightly deviating the drug release at all time points and also still need to improve the flow of blend. The trail TM 11 showed improved drug release than reference product at all time points and also showed excellent free flow of blend and results found satisfactory. The results of the same were given in table 16 and the graph of the same was showed in figure 09.

Table-16: *In-vitro* dissolution data for trails TM 09-TM 11 Vs Reference product.

Time in minutes	Reference product	% Cumulative Drug Release (%RSD)		
		TM 09	TM 10	TM 11
05	82 ± 1.84	70 ± 1.54	78 ± 1.21	84 ± 0.67
10	87 ± 1.23	80 ± 1.48	83 ± 1.29	90 ± 1.25
15	93 ± 1.08	87 ± 1.19	89 ± 1.36	96 ± 1.19
30	96 ± 1.24	91 ± 1.24	93 ± 1.58	99 ± 0.94

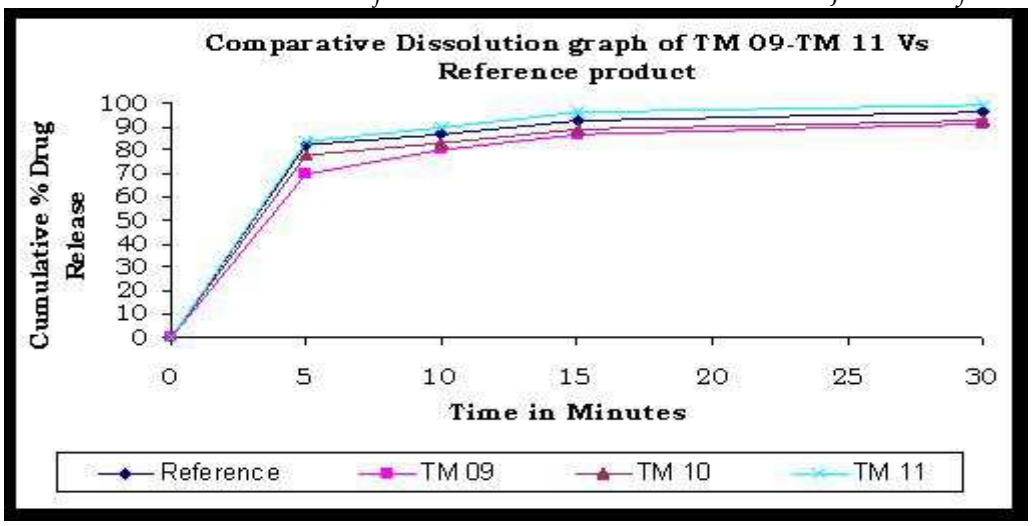

Figure 09: Comparative dissolution graph of TM 09-TM 11 Vs Reference product.

The trail TM 11 is considered as optimized formulation as part of dissolution and flow properties. Next as per our concern their needs to mask the unpleasant taste of the drug. So further two more trails i.e. TM 12-TM 13 was formulated and given to five human volunteers to study the organoleptic characters of the drug product.

The trails TM 12 is prepared with neotame is taste masking agent and tutti frutti as flavor. The results showed that out of five volunteers, four volunteers said that taste and flavor was good and one volunteer said that taste and flavor was very good. So further trail was planned with same composition and sweetener & flavor was increased too little higher side.

The trail TM 13 showed that out of five volunteers, one volunteer said that taste & flavor was good and four volunteers said that taste & flavor was very good. So the trail TM 13 is considered as optimized formulation in concern of flow properties, disintegration, dissolution and organoleptic characters and results of the same was showed in table 17.

Table 17: Flavor and Sweetener optimization trails.

Volunteers ↓	Formulation trails	
	TM 12	**TM 13**
1	XX	XX
2	X	XX
3	X	XX
4	X	X
5	X	XX

X= good; XX; very good

The comparative dissolution was done for optimized formulation TM 13 in 0.1N HCl and pH 7.4 phosphate buffer (saliva pH). The results showed that the release of the drug was exactly similar in both medias i.e. 0.1N HCl and pH 7.4

phosphate buffer and there is no noticeable change was observed in pH 7.4 phosphate buffer. The results of the same were given in table 18 and the graph of the same was shown in figure 10.

Table-18: Comparative dissolution data of TM 13 in 0.1N HCl and pH 7.4 phosphate buffer.

Time in minutes	% Cumulative Drug Release	
	0.1N HCl	pH 7.4 phosphate buffer
05	85	84
10	90	89
15	95	95
30	99	99

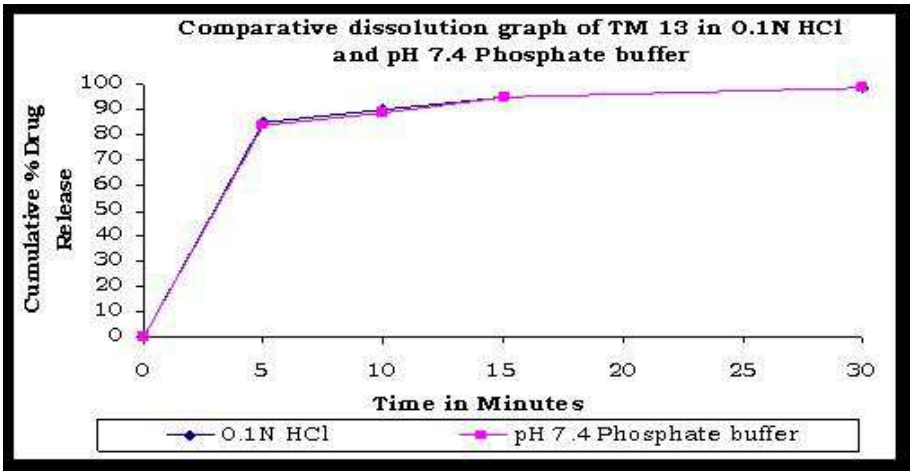

Figure 10: Comparative dissolution graph of TM 13 in 0.1N HCl and pH 7.4 phosphate buffers.

Stability Studies:

The stability studies place a major role in the development of dosage form and these were conducted to predict the shelf life of the drug product. From the stability data it revealed that the drug was stable for a period of 3 months at accelerated condition and the results of all parameters were found satisfactory. The results of same were given in table 19 and the comparative graph of initial with 1st, 2nd, 3rd month stability was shown in figure 11 and physical observation of tablets were shown in figure 12-13.

Table-19: Stability data for Optimized formulation TM 13.

Name of Test	Initial	1st month	2nd month	3rd month
Appearance*	Complies	Complies	Complies	Complies
Dissolution				
05 minutes	85	84	85	83
10 minutes	90	89	91	89
15 minutes	95	95	96	94
30 minutes	99	99	99	98
Assay	99.7	99.7	99.6	99.8

Friability	0.12 ± 0.08	0.10 ± 0.04	0.18 ± 0.06	0.15 ± 0.05
Disintegration	15 ± 0.62	13 ± 0.09	16 ± 0.95	17 ± 0.49
Dispersion time	10 ± 0.24	11.8 ± 0.33	11.5 ± 0.31	11 ± 0.15

Data presented as Mean ± SD

*White to off white colored round, biconvex uncoated tablets plain on both sides.

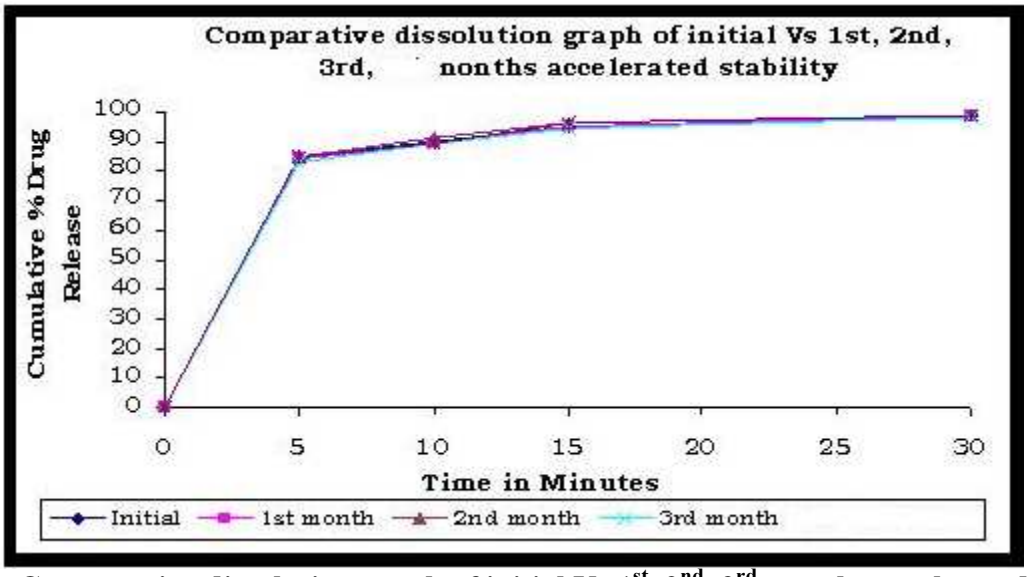

Figure 11: Comparative dissolution graph of initial Vs 1st, 2nd, 3rd months accelerated stability.

Physical Observation

Figure 12: Initial tablets packed in Alu-Alu.

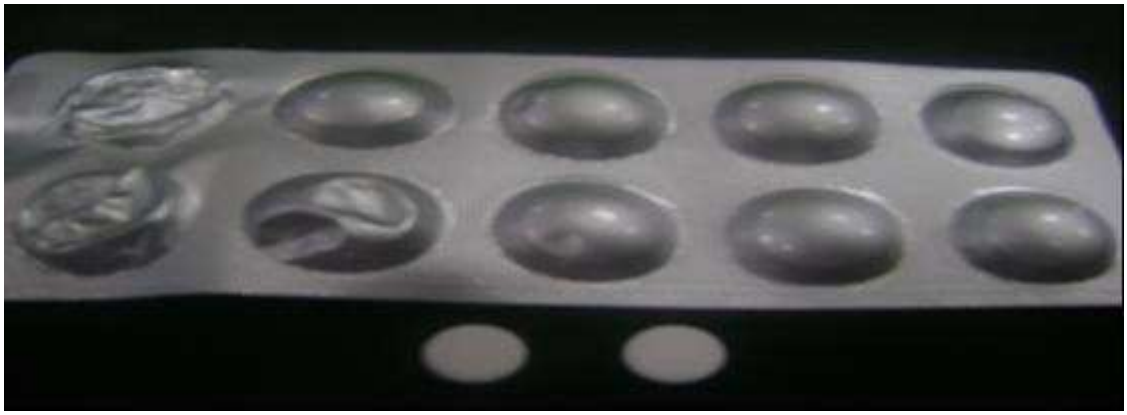

Figure 13: Tablets after 33M stability.

Physical observation of tablets: By considering all results and stability data shown in figure 12-13, it was concluded that the trail TM 13 is most stable and is meeting the predetermined specifications of dissolution, assay, friability, disintegration time and dispersion time for a period of 3 months at accelerated conditions.

Conclusion

Tablets prepared with Pharmaburst as co-processed excipients are the most suitable disintegrants for the preparation of mouth dissolving tablets. The tablets exhibited good i*n vitro* dispersion and water absorption ratio, showed better disintegration and drug release. Prepared tablets disintegrate within few seconds without need of water; thereby enhance absorption leading to increased bioavailability. The optimized test formulation showed superior drug release to reference product and also demonstrated good stability over a period of 6 months. Thus the present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and increased patient compliance.

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