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FORMULATION, DEVELOPMENT AND EVALUATION OF FAST DISSOLVING TABLETS OF TERFENADINE

Ragini Gour*, Ms. Chanchal Jain, Dr. Navjot Singh
NRI institute of pharmacy (NIP) Bhopal M.P.

Abstract:
Terfenadine is an antihistamine formerly used for the treatment of allergic conditions. Terfenadine, an H1-receptor antagonist antihistamine, is similar in structure to astemizole and haloperidol, a butyrophenone antipsychotic. The active metabolite of terfenadine is fexofenadine. The aim of present work was to develop fast dissolving tablets of Terfenadine by direct compression method using different binders Sodium starch glycolate, croscarmellose sodium and microcrystalline cellulose. The prepared tablets were evaluated for parameters such as hardness, friability, drug content, weight variation, in-vitro disintegration time, in vitro dissolution studies and stability studies. Disintegration Time of different prepared formulation F1, F2, F3, F4, F5 and F6 was found to be 105±4, 98±3, 95±5, 68±4, 43±2, and 55±1sec., the minimum Disintegration time was found in formulation F5 (43±2 sec.), select as optimized formulation.When the regression coefficient values of were compared, it was observed that 'r^2' values of Higuchi release kinetics was maximum i.e.0.992 hence indicating drug release from formulations was found to follow Higuchi release kinetics.

Keywords: *Fast dissolving tablets, Superdisintegrants, Terfenadine, Crosspovidone, Sodium carboxy methyl cellulose. Direct Compression.*

Corresponding author:
RaginiGour,
raginigour81@gmail.com

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INTRODUCTION:

Formulation of drugs into a presentable form is the basic requirement and need of today. The dosage form is a mean of drug delivery system, used for the application of the drug to a living body. Various type of dosage forms are available such as tablets, syrups, suspensions, suppositories, injections, transdermal and patches having a different type of drug delivery mechanisms. These classical/ modern dosage forms have some advantages and disadvantages. Therefore, the development of an ideal drug delivery system is a big challenge to the pharmacist in the presence scenario. In order to get the desired effect, the drug should be delivered to its site of action at such rate and concentration to achieve the maximum therapeutic effect and minimum adverse effect. For the development of a suitable dosage form a thorough study about the physicochemical principles that governs a specific formulation of a drug should be subjected [1].

Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients is the difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention [2].

The problem of swallowing is a common phenomenon in a geriatric patient due to fear of choking, hand tremors, dysphasia and in young individuals due to underdeveloped muscular and nervous systems and in schizophrenic patients which leads to poor patient compliance. Approximately one-third of the population (mainly paediatric and geriatric) has swallowing difficulties, resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention [3].

Unite d States Food and Drug Administration (USFDA) defined fast dissolving tablet (FDT) as “a solid dosage form containing a medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue” [3]

Fast dissolving drug delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for the pediatric and geriatric patient. These tablets are designed to dissolve or disintegrate rapidly in the saliva generally less than 60 seconds [4, 5]. To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage forms known as orally disintegrating (dispersible) tablets (ODTs) or Fast disintegrating (dissolving) tablets (FDTs) or mouth melting tablets (MMTs) or mouth dissolving tablets(MDTs), immediate release tablets which disintegrate rapidly in saliva, usually in a matter of seconds, without the need to take water.

Fast disintegrating tablets (FDTs) have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. Recent advancements in novel drug delivery system (NDDS) aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration in order to achieve better patient compliance. One such approach is “fast disintegrating tablet.” Many patients find it difficult to swallow tablets and hard gelatin capsules that result in high incidence of noncompliance and ineffective therapy.

Terfenadine is used as Anti-Allergic Agents; Anti-Asthmatic Agents H1 Antagonists In Present Investigations fast disintegrating tablets of Terfenadine can be prepared by direct compression method using superdisintegrants like crospovidone (CP), croscarmellose sodium (CCS), sodium starch glycolate (SSG) and combination of super-disintegrants in different concentrations.

MATERIAL AND METHODS:

Preparation of tablets of Terfenadine

Fast dissolving tablets of Terfenadine (60mg)were prepared by direct compression method after incorporating different superdisintegrants such as, croscarmellose sodium (Ac-Di-Sol) 10, 15, and 20 mg, crospovidone in different concentrations 10, 15, and 20 mg for optimization of best formulation [6]. The ingredients given below were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh 60.

Magnesium stearate (6mg) as lubricant and talc (5 mg) as glidant and Microcrystalline cellulose as bulking agent (109, 104, 99, 109, 104 and 99mg) were added in a final step and mixed, this blend was subjected to analysis of pre-compression parameters which included Angle of repose, Bulk density, Tap density, Carr's index and Hausner's ratio.

The Blend was compressed on 8 mm (diameter) fat punches on a 'Rimek mini press 16 station rotary compression machine. Six formulations of Terfenadine granules were prepared and each formulation contained one of the three disintegrant in different concentration. Each tablet weighing 200 mg was obtained. Composition of tablets is mentioned in Table no 1.

Table 1: Composition of Terfenadine fast dissolving tablets

Ingredients (mg)	Formulation code					
	F1	F2	F3	F4	F5	F6
Terfenadine	60	60	60	60	60	60
Sodium Starch glycolate	20	25	30	-	-	-
Croscarmellose sodium		_	_	20	25	30
Microcrystalline cellulose	109	104	99	109	104	99
Talc	5	5	5	5	5	5
Magnesium stearate	6	6	6	6	6	6
Total weight	200	200	200	200	200	200

Evaluation of Precompression Parameter

Angle of repose (θ): The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane[7].

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} (h/r)$$

Where, θ is the angle of repose, h is the height, r is the radius.

The granules were allowed to flow through the funnel fixed to a stand at definit height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined [45]. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

$$\text{LBD (Loose Bulk Density)} = \frac{\text{Mass of Powder}}{\text{Volume of Packing}}$$

$$\text{TBD (Tapped Bulk Density)} = \frac{\text{Mass of Powder}}{\text{Tapped Volume of Packing}}$$

Carr's Compressibility index: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula:-

$$\text{Carr's Index \%} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100$$

Hausners ratio: It is determined by comparing tapped density to the bulk density by using following equation:-

Housner's ratio = Tapped bulk density/loose Bulk density

Hausner's ratio value <1.25 shows better flow properties

Evaluation of post compression Parameter

Shape and colour of tablets

Uncoated tablets were examined under a lens for the shape of the tablet and colour was observed by keeping the tablets in light [8].

Thickness test

Three tablets were picked from each formulation randomly and thickness was measured individually [9]. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan).

Weight variation test

Twenty tablets were selected randomly from each formulation and average weight was determined [10]. The tablets were weighed individually and compared with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed.

Hardness test

The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg/cm^2 [11].

Friability test

For this, 20 tablets were taken from each formulation and the friability was determined using Roche friabilator. The equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated [12]. The friability was determined as the mass loss in percent according to Equation:-

$$\%Friability = (Loss\ in\ weight/Initial\ weight) \times 100$$

The test complies if tablets not loss more than 1% of their weight.

Uniformity of drug content

The test is mandatory for tablets with 10 mg or less weight of active ingredient [13]. Ten randomly selected tablets from each formulation (F1 to F6) were finely powdered and Drugequivalent to 10 mg of drug dissolved in 10 ml phosphate buffer pH 6.8) sonicate it for 20 minutes, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper No. 41. From this Solution take 1 ml and Diluted up to 100 ml with 0.1 N HCl and the drug content was determined spectrophotometrically at 260nm.

***In vitro* dissolution rate studies**

The prepared tablets were evaluated for *in vitro* drug release. The drug release studies were carried out using USP XXII paddle type Dissolution test apparatus [14]. The dissolution study was carried out in 900 ml dissolution medium which was stirred at 50rpm maintained at 37±0.2°C. The scheme of using the simulated fluids at different timing was as follows:

A tablet placed in dissolution media (900 ml) at 37±0.2°C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 10ml 0.1 N HCl. The samples withdrawn were assayed spectrophotometrically at 260nm using UV visible spectrophotometer.

RESULTS AND DISCUSSION:

The loose bulk density (LBD) and Tapped bulk density (TBD) of the powders of different formulations were evaluated before the compression of powders in to tablets. The bulk density and the tapped density for all the formulations varied from 0.413 to $0.452gm/cm^3$ and 0.522 to $0.552gm/cm^3$ respectively.

Different formulation of Terfenadine fast dissolving tablets were prepared and evaluated for pre and post compression parameters. The values obtained lies within the acceptable range. The difference exists between the bulk density and tapped density found to be very few. This result helps in calculating the % compressibility of the powder. The result of Hausner's ratio of all formulations ranges from 1.221 to 1.271. Results of Hausner's ratio of all formulations were shown in Table no 2 which indicates that the flow ability of all the formulation.

The results of the Compressibility index of all the formulations ranges from 22.12% to 27.08%. Results of Compressibility index of all the formulations were shown in the Table no 8.1. Results clearly showed that the flow ability of all the formulations was good and also the powder had good compressibility.The thickness of the tablets was reported in the micrometer (mm).The thickness of tablet indicates that, die fill was uniform. The thickness depends on the size of the punches (8 mm) and the weight of one tablet (200mg). The average weight of each formulation was recorded in shown in Table no 2. The value of thickness ranges between 1.25±0.02 to 1.35±0.02mm.

Friability determines the strength of the tablets. The values of friability test were given in the Table no 3. The friability for all the formulations was below 1% indicating that the friability was within the prescribed limits. The results of friability test indicate that the tablet possesses good mechanical strength. The friability value ranges from 0.558±0.036 to 0.765±0.041. The mean hardness values were measured for all the formulation using Monsanto hardness tester. The results were tabulated in Table no 3. The hardness value ranges from 3.2±0.2 to $3.5±0.1kg/cm^2$.

Twenty tablets were randomly selected from each formulation and evaluated. The average weight of each formulation was recorded and is shown in Table no 8.2. The obtained data were almost uniform. The values of tablets average weight ranging from 198±5 to 206±4mg. All the tablets passed weight variation test as the % weight variation was within the USP Pharmacopoeia's limits of ±5% of the weight. The % drug content of all the formulated tablets were found within the limit. % drug content value was within

95.65±0.32% to 99.12±0.32%.The results within the range indicate uniform of mixing. The Table no 3 shows the % drug content in each formulation.
Disintegration Time of different prepared formulation F1, F2, F3, F4, F5 and F6 was found to be 105±4, 98±3, 95±5, 68±4, 43±2, and 55±1sec., the minimum Disintegration time was found in formulation F-5 (43±2 sec.), select as optimized formulation Table no 4.When the regression coefficient values of were compared, it was observed that 'r^2' values of Higuchi release kinetics was maximum i.e.0.992 hence indicating drug release from formulations was found to follow Higuchi release kinetics table no. 5, 6.

Table 2: Results of pre-compression parameters of Terfenadine

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	0.452	0.552	22.12	1.221
F2	0.413	0.522	26.39	1.264
F3	0.432	0.545	26.16	1.262
F4	0.436	0.546	25.23	1.252
F5	0.421	0.535	27.08	1.271
F6	0.425	0.537	26.35	1.264

Table 3: Results of post-compression parameters of all formulations

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)
F1	3.2±0.2	0.658±0.015	202±4	1.26±0.02	95.65±0.32
F2	3.5±0.1	0.632±0.025	195±6	1.28±0.03	96.12±0.14
F3	3.4±0.3	0.587±0.023	198±5	1.32±0.01	95.74±0.25
F4	3.4±0.2	0.687±0.047	206±4	1.34±0.04	98.85±0.32
F5	3.2±0.1	0.558±0.036	204±3	1.35±0.02	99.12±0.32
F6	3.4±0.4	0.765±0.041	203±2	1.25±0.02	98.45±0.15

Table 4: Results of disintegration time parameters of all formulations

Formulation code	Disintegration Time (Sec.) Mean ± SD
F1	105±4
F2	98±3
F3	95±5
F4	68±4
F5	43±2
F6	55±1

***Average of three determinations (n=3)**

Table 5: *In-vitro* drug release data for optimized formulation F5

Time (min)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	1	0	35.45	1.550	64.55	1.810
5	2.24	0.698	65.58	1.817	34.42	1.537
10	3.16	1	79.95	1.903	20.05	1.302
15	3.87	1.176	98.85	1.995	1.15	0.061

Table 6: Regression analysis data

Batch	Zero Order	First Order	Higuchi
	r^2		
F5	0.957	0.861	0.992

CONCLUSION:

The results of this study suggest that terfenadine fast dissolving tablets are a suitable alternative to traditional tablets for the delivery of terfenadine. The fast dissolving tablets are able to deliver the same amount of terfenadine within the same timeframe as traditional tablets, while also providing patient convenience and improved patient compliance. Therefore, terfenadine fast dissolving tablets can be used as a viable alternative to traditional tablets for the delivery of terfenadine.

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