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Formulation and Evaluation of Fast Disintegrating Tablets of ANTICHOLINERGIC BRONCHODILATORS

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ABSTRACT

Fast disintegrating tablets have possible advantages over usual dosage forms, with improved patient observance, convenience, bioavailability and rapid onset of action. They are good substitute for drug delivery to geriatric and paediatric patients. They have major advantages of both solid and liquid dosage forms, as they remain solid during storage, which assist in stability of dosage forms and transform into liquid form within few seconds after its administration Thus FDT has great scope for being immediate drug delivery. Tiotropium bromide and cetirizine hydrochloride are used as a model drug in the preparation of formulation. It is generally used for the treatment of Asthma. It is safe well tolerated. The study began with the preformulation characterization of drug which involves determination of melting point and development of suitable analytical method for the estimation of drug. All the evaluation parameters were found to be in range as compared with standard. All the drugs and excipients used in preparation of formulation was found to be compatible with each-other. Fast disintegrating tablets were prepared by direct compression method. The disintegration time of tablets of drugs prepared by direct compression were found to be in the range of 30-40 seconds. Tablets prepared with highest percentage of Crospovidone i.e. F15 showed the best result. Results of dissolution study showed that more than 50% of the drug was released within the first 5 minutes.

Key-words: Tiotropium Bromide, Cetirizine Hydrochloride, Fast Disintegrating Tablets, Crospovidone

INTRODUCTION

Oral drug delivery is the most common and preferred route of drug delivery among all the routes that have been explored for the general delivery of drugs via varied pharmaceutical product of different indefinite quantity forms (Prakash et al., 2011). Among all the dosage form the most popular solid dosage forms are tablet and capsule. Increasing in popularity could also be partly attributed due to its simple and ease of administration. This is also due to its ancient belief that by oral administration the drug is still absorbed because the foodstuffs that are ingested daily (Chang et al., 2000). One drawback of these dosage forms however is the difficulty to swallow (Ishikawa et al.,1999).

Regardless of increasing attention in controlled release drug delivery systems, the most common form of dosage form i.e. tablets are those supposed to be enclosed whole and to disintegrate and unreleased their medicaments quickly within the gastro enteral tract. In additional recent years, increasing attention has been paid to formulating not solely fast dissolving tablets that are indented to dissolve and/or disintegrate quickly within the mouth.

To meet these medical needs, pharmaceutical technologists have worked hard to produce a revolutionary type of oral dosage form called the Fast Dissolving Tablet (FDT), which dissolves and disintegrates swiftly in saliva without the use of water. The fast-dissolving tablets normally disintegrate in 15 to 60 seconds in the oral cavity. The faster the medicine dissolves in solution, the faster it is absorbed and begins to have therapeutic effects. The invention of fast-dissolving tablets also allows for market line expansion (Seager et al., 1998).

FDT is defined by the USFDA as "a solid dosage form containing a medical substance or active component that disintegrates and dissolves fast when placed upon the tongue, usually within a matter of seconds," with disintegration times varying from a few seconds to around a minute.

Direct compression, wet granulation, compression moulding, volatilization, vacuum drying, and freeze-drying are some of the processes accessible. They entail a variety of methods, such as the use of large amounts of hydrophilic disintegrating agents in effervescent combinations, which allow dosage forms to disintegrate fast in the patient's mouth when they come into contact with saliva (Sanjay et al. 2002). There are over fifteen fast-dissolving products available on the market today. This tablet contains chemicals that speed up the pace of tablet disintegration in the oral cavity, and is more accurately referred to as fast dissolving tablets because it takes no more than 60 seconds for the tablet to completely disintegrate (Porter et al., 2001).

Asthma is a prevalent chronic obstructive pulmonary disease characterized by a complicated combination of airflow restriction, bronchial hyperresponsiveness, and underlying inflammation (Centers for Disease Control and Prevention [CDC], 2009). According to a survey, asthma affects 22 million people worldwide, with over half of them living in the United States.6 million of these people are youngsters (National Institutes of Health [NIH], 2005).It affects approximately 300 million people worldwide, with the number expected to rise to 400 million by 2025. (Masoli et al., 2004). Asthma medications are divided into two categories: controllers and relievers. Controllers are long-term drugs that are taken every day to keep asthma under control, primarily through anti-inflammatory effects. Inhaled and systemic glucocorticoids, as well as leukotriene modifiers, have long been used to treat coexisting illnesses (e.g., allergic rhinitis) without fear of interfering with albuterol's bronchodilatory impact or exacerbating asthma on its own.

As a result, the current study will seek to create and analyze a fast dissolving tiotropium bromide and cetirizine hydrochloride formulation.

MATERIALS AND METHODS

Materials

Jai Radhe Sales, Ellis Bridge, Ahmedabad, India, provided tiotropium bromide as a free sample. Himedia Laboratories Pvt. Ltd., Mumbai, India, provided the cetirizine hydrochloride. Loba chemicals Pvt.Ltd., Mumbai, India, provided talc, sodium starch glycollate, crospovidone, and magnesium stearate. Yarrow chem. Products, Mumbai, India, provided microcrystalline cellulose.

Methods

Preparation of fast disintegrating tablets

The direct compression method was used to make fast disintegrating tablets because it has numerous advantages:

- It is the simplest way to make tablets,
- It can accommodate high doses,
- It uses standard equipment,
- It uses generally available excipients.

Inhaled β2-agonists with inhaled glucocorticoids, sustained-release theophylline, cromones, and anti-IgE. Tiotropium bromide is a new muscarinic antagonist that has been developed for the treatment of chronic obstructive pulmonary disease (COPD) (COPD). *In vitro*, tiotropium bromide has a more potent inhibitory effect than atropine or ipratropium bromide against cholinergic nerve-induced contraction of guinea pig and human airways, with a later onset. Tiotropium bromide, on the other hand, dissociates extremely slowly after washout compared to atropine and ipratropium bromide. It also protects against cholinergic bronchial constriction for more than 24 hours. This shows that tiotropium bromide will be a beneficial bronchodilator, especially in COPD patients, and that it might be used on a daily basis (Barnes et al., 1995).

In terms of palatability, its insolubility in water and blend taste make it a great candidate for fast disintegrating tablets. Asthmatic patients must rigorously adhere to the dose schedule in order to avoid subtherapeutic concentrations. Even when traveling or in other situations when there is no access to water, fast dissolving/ disintegrating tablets will prevent you from missing a dosage. In the formulation of oral dosage forms, poor dissolving of somewhat insoluble medicines has been a challenge. Aspects such as absorption and bioavailability are hampered as a result.

In individuals with mild-to-moderate asthma, cetirizine hydrochloride has a considerable bronchodilator effect and can be processed in a limited number of stages.

The fast-dissolving tablets were made with coprocessed superdisintegrants (Ac-disol with crospovidone and sodium starch glycolate with crospovidone) and tested for compression qualities before and after compression. The parameters measured were compared to those of tablets made from a physical mixture of superdisintegrants.

The tablets were made on a single punch tablet machine (Cadmach, Ahemdabad) that produced flat sided tablets with a diameter of 5 mm and a weight of 128 mg apiece. Each batch consisted of a minimum of 50 pills. Prior to compression, mass-volume relationships (bulk density, tapped density, Hausner's ratio, compressibility index) and flow parameters of tablet blends were assessed (angle of repose). Different approaches were used to create the formulations.

Technology Followed – Superdisintegrant Addition

The superdisintegrants (Ac-di-sol, sodium starch glycolate and crospovidone) in varying concentration (1-5% w/w) are used to develop the tablets. All the ingredients are shown in Table 1 were passed through sieve no. 60 and were co- grounded in a glass pestle motor (Sushil 2017).

EVALUATION OF TABLETS

Pre-compression characterization

The quality of tablet, once formulated by rule, was generally dictated by the quality of physicochemical properties of blends. There were many formulations and process variables involved in mixing steps and all these can affect the characteristics of blend produced. The characterization parameters for evaluating the flow property of mixed blends includes bulk density, tapped density, Hausner's ratio, compressibility index and angle of repose.

Table 1: Formulation of tablets with superdisintegrants

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**
Tiotropium Bromide	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18
Cetirizine Hydrochloride	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Ac-di-sol	1	2	3	4	5	-	-	-	-	-	-	-	-	-	-
Sodium starch glycollate	-	-	-	-	-	1	2	3	4	5	-	-	-	-	-
Crospovidone	-	-	-	-	-	-	-	-	-	-	1	2	3	4	5
Avicel PH102	55	54	53	52	51	55	54	53	52	51	55	54	53	52	51
Lactopress	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25
Mannitol	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2

Bulk density (Martin *et al*., 2002)

The bulk density (ρ_b) of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the interparticle void volume.

Method: Bulk density of a powder is determined by pouring the blend into a graduated cylinder. The bulk volume and weight of the powder was determined.

The bulk density was calculated using the formula:

Bulk density = Mass of an untapped powder sample / Bulk volume $\rho_b = M / V_b$

Tapped density (Marshall *et al*., 1987**)**

The tapped density (ρt) is an increased bulk density attained after mechanically tapping a container containing the powder sample.The tapped density is obtained by mechanically tapping a graduated measuring cylinder containing a known mass of powder sample (M) for 100 times. After observing the initial powder volume, the measuring cylinder is mechanically tapped, and minimum volume (Vt)readings occupied by powder in the graduated cylinder are taken until little/ no further volume change is observed.

Tapped density = Mass of an untapped powder sample / Tapped volume

$\rho_b = M / V_t$

Angle of repose (Ji)

It is the maximum angle possible between the surface of a pile of powder and the horizontal plane. It is measured according to the "fixed funnel and free standing cone method". A funnel was clamped with its tip 7 cm above a graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the cone thus formed just reached the tip of the funnel (Fiese EF et al., 1987).

The mean diameters of the base of the powder cones were determined and the tangent of the angle of repose was calculated using the equation:

tan = h / r where,
= angle of repose

h = height of tip of funnel from base

r = radius of base of the heap of the powder

% Compressibility index(Subrahmanyam, 2000, Shariff et al., 2007)

% Compressibility = tapped density - bulk density / tapped density x 100

Hausner ratio (Tang L *et al*., **2001)**

It is an indirect index of ease of powder flow. It is calculated by the following formula: Hausner ratio = tapped density / bulk density If value obtained is less then 1.25, it indicates powder falls in the category of good flow.

Carr's index (CI) (Tang L *et al*., **2001**)

The Carr's index is an indication of the compressibility of a powder. It is an indirect measure of bulk density and cohesiveness of material.

Relationship between Carr's index (CI) and Hausner ratio is: Hausner ratio = 100/ (100 - Carr'sindex)
Also, CI = Initial volume – final volume / final volume X 100

Values below 15% indicate a powder with usually good flow characteristics, whereas those above 25% indicate poor flowability.

EVALUATION OF TABLETS

Drug content

For the drug content ten tablets were weighed, crushed and powdered. An amount of the powder equivalent to 100 mg of caffeine was taken and dissolved in 100 ml of pH 6.8 buffer, filtered, diluted suitably and analyzed for drug content at 271 nm using UV-Visible double beam spectrophotometer (UV 2201 SYSTRONICS).

Size and shape (Indian Pharmacopeia, 1997)

These include diametric size, shape and thickness. Diameter and thickness were measured in micrometer using digital micrometer.

Tablets hardness (Gennaro, 2000)

Hardness was measured using Monsanto tablet hardness tester. The force required to crush the tablet was recorded as hardness in Kg/cm^2.

Weight variation (Indian Pharmacopeia, 1997)

Twenty tablets were weighed individually using digital weighing balance and their average weight was determined. Then individual tablet weight was compared with average weight.

Friability (Indian Pharmacopeia, 2000)

Friability of the tablets was determined was determined using Roche Friabilator. In this, the tablets were subjected to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre-weighed sample of tablets was placed in the friabilator and subjected to 100 revolutions. Tablets were de-dusted using a soft muslin cloth and reweighed.

The friability is given by the formula:

% Friability = (Wi – Wf/ Wi) X 100 Where,

Wi = initial weight of tablets Wf = final weight of tablets

In vitro Disintegration test

The disintegration time was measured using disintegration test apparatus. One tablet was placed in each tube of the basket. The basket with the bottom surface made of a stainless-steel screen (mesh no. 10) was immersed in water bath at 37 ± 2ºC. The time required for complete disintegration of the tablet in each tube was determined using a stop watch. To be complied with the Pharmacopoeial standards, dispersible tablets must disintegrate within 3 mins when examined by the disintegration test for tablets.

Results and Discussion Compatibility studies

Infrared spectroscopic study: Fourier transformed (FTIR) spectrum of Diclofenac, Drug with different excipients were obtained on a FTIR (Perkin-Elimer) using the KBr disk method. From the comparative FTIR spectral study, for compatibility study of drugs powder, and excipient. All the major peaks related to Tiotropium bromide**,** Cetirizine hydrochloride, Crospovidone were retained in FTIR spectrum of the physical mixture, indicating an absence of any interaction. It can be concluded that there was no significant difference in the FTIR spectra of physical mixtures when compared to FTIR spectra of individual components.

Pre-compression characterization

The Bulk density of all the formulations were within the range of 0.408±0.02 g/ml and Tapped density was found to be in the range of 0.436±0.01 g/ml (good flow property). The Angle of repose of powder blends of all formulation was found to be in the range of 25.22±1.06 (good flow property). The calculated % Compressibility index of formulations was found to within the range of 6.422±1.03 (Excellent). The calculated Hausners ratio of all the formulations was found to be in the range of 1.068±0.01 (good flow property). The values of pre- compressional parameters evaluated were within the prescribed limits and indicated good free flowing properties.

Post compression parameters

After compression of powder blends, the prepared tablets were evaluated for organoleptic characteristics like color, odor, diameter, thickness and physical characteristics like hardness, friability, disintegration time, wetting time, dispersion time.

Drug content

Drug content was found to be in the range of 95 to 99%, which is within acceptable limits.

Size and shape (Indian Pharmacopeia, 2007)

The shape of the prepared tablet was found to be round shape.

Tablets hardness (Gennaro, 2000)

Hardness was measured using Monsanto tablet hardness tester. Since mechanical integrity is of paramount importance in successful formulations,

hence the hardness of tablets was determined and was found to be in the range of 4-5 Kg/cm^2.

Weight variation (Indian Pharmacopeia, 2007)

Tablets passes the weight variation test as per the IP. Percent weight variation was observed between 4.0 and 6.1 which were well within the acceptable limit for uncoated tablets as per United States Pharmacopoeia. It is well known to formulation scientists that the tablets with more hardness show longer disintegration time.

Friability (Indian Pharmacopeia, 2000)

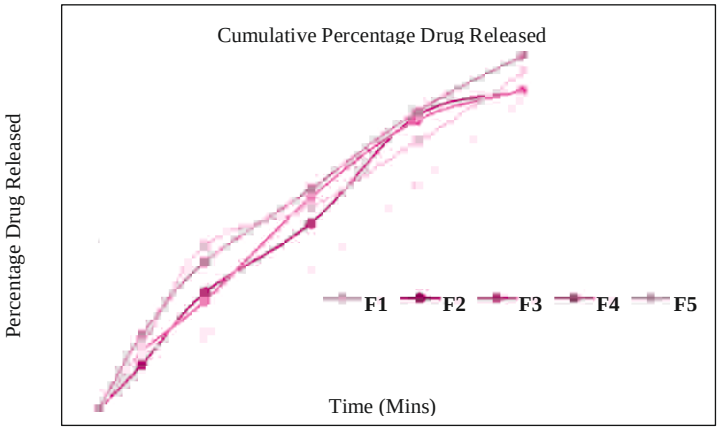
Friability was observed between 0.40 and 0.59 %, which were below 1% indicating sufficient mechanical integrity and strength of prepared tablets. The results of friability indicate that the tablets were mechanically stable and can withstand rigors of transportation and handling.

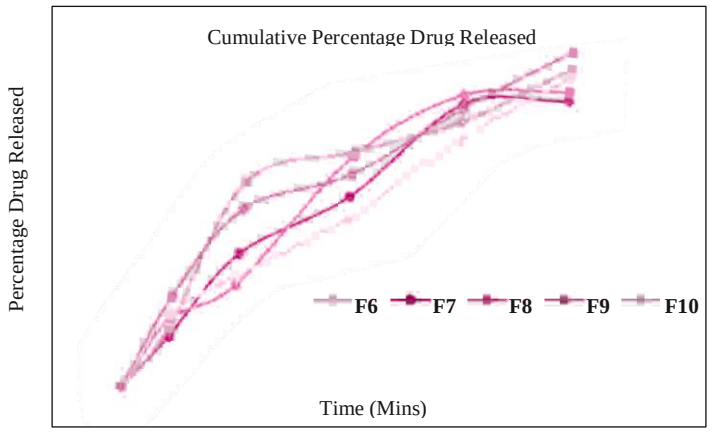
In vitro Disintegration test

Disintegration time is very important for disintegrating tablets, which is desired to be less than 10 minutes. This rapid disintegration assists drug absorption and thus promoting bioavailability. In vitro disintegration time was determined using disintegration test apparatus without disk for six tablets. The disintegration medium was 900 mL of distilled water kept at 37 ± 0.5ºC and stirred at a rate of 30±2 cycles/min. The time was measured in seconds for complete disintegration of the tablet with no palpable mass remaining in the apparatus. The test was carried out in triplicate. The disintegration time for formulations was found to be 30 seconds. The results of disintegration of all the tablets were found to be within prescribed limits and satisfied the criteria.

Dissolution studies

In vitro drug release study was performed in *0.1 N HCl* pH 1.2 solution following the reported method (Singh et al., 2015). The release of formulated FDTs was determined using USP eight-stage dissolution testing apparatus-2 (paddle method) (Lab, India). The dissolution test was performed using 500 mL of phosphate buffer solution, pH 1.2 at 37 ºC and 50 rpm. A sample (5 mL) of the solution was withdrawn from the dissolution apparatus at specific time intervals, and the samples were replaced with fresh dissolution medium. The samples were filtered through Whatman filter paper. Absorbance of these solutions was measured at 243 nm using a double beam UV spectrophotometer (UV-1800 Shimadzu). Cumulative percentage (%) of drug release was calculated using standard plot of tiotropium bromide.





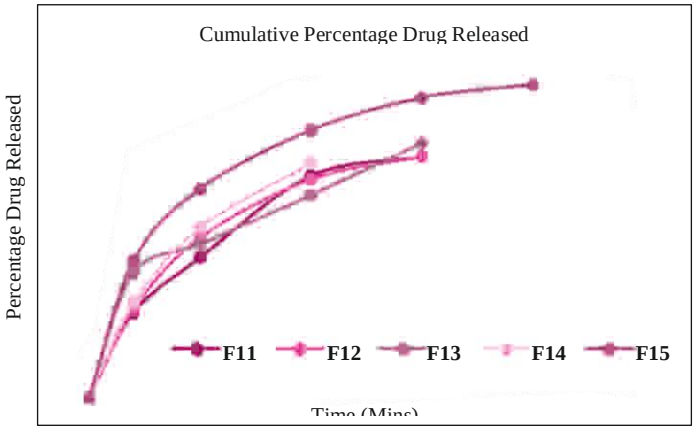


Figure 1. *In vitro* dissolution profile of optimized formulation

In vitro dissolution studies on the promising formulations (F1- F5), (F6-F10) and (F11-F15) was carried out. The comparative dissolution graph was plotted separately and analyzed for best formulation.

In-vitro dissolution studies of the prepared samples were performed in pH values of pH 1.2 for 20 mins. The complete in- vitro dissolution study was divided in three main sections:

i). Drug released study of optimized formulation F1-F5.

ii). Drug released study of optimized formulation F6-F10.

iii). Drug released study of optimized formulation F11-F15.

In the preliminary studies (F1-F5), results of dissolution study showed that less than 20% of the drug was released within the first 5 minutes. Slow release rate of tablets is not accepted for drugs that are required to be released within 15 minutes. Results of Ac-di-sol used excipients showed very less percentage of drug released.

In the second phase Sodium starch glycollate (F6-F10) was used. Results of dissolution study showed that less than 40% of the drug was released within the first 5 minutes. Slow release rate of tablets is not accepted for drugs that are required to be released within 15 minutes. Results of Sodium starch glycollate excipients showed very less percentage of drug released.

In the third part (F11-F15) of dissolution investigation, dissolution study of prepared tablets was carried out. Tablets prepared with highest percentage of Crospovidone i.e. F15 showed the best result. Results of dissolution study showed that more than 50% of the drug was released within the first 5 minutes. More release rate of tablets is accepted for drugs that are required to be released within 15 minutes. Results of Crospovidone showed very more percentage of drug released.

Stability of prepared tablets

Stability studies were carried out according to ICH guidelines. In this study, coated tablets were sealed in aluminum packaging coated inside with polyethylene, and three replicates were kept in a humidity chamber maintained at 40 ± 2^0 C and $75 \pm 5\%$ RH for three months (Chaudhary *et al*., 2009). Samples were collected after three months of storage and analyzed for drug content and *in -vitro* dissolution rate. After successful completion of 90 days, the sample were subjected to dissolution studies as per the method described above to verify whether any changes in dissolution profiles took place due to stability issues.

Stability studies of the prepared tablets were carried out at 40 ± 2^0 C and $75 \pm 5\%$ RH for three months to assess their potential utility. After storage for three months, the tablets were subjected to drug content and *in-vitro* dissolution studies. Results of the stability study showed that there was no marked difference in drug content and dissolution profiles of tablets before and after storage.

SUMMARY AND CONCLUSIONS

From the results of the prepared formulations, following points can be concluded:

1. The study began with the preformulation characterization of drug which involves determination of melting point and development of suitable analytical method for the estimation of drug. All the evaluation parameters were found to be in range as compared with standard.

2. Drug excipients interaction studies carried using FTIR analysis indicated that drug is compatible with the selected formulation excipients. All the drugs and excipients used in preparation of formulation was found to be compatible with each-other.

3. Fast disintegrating tablets were prepared by direct compression method. Preliminary fifteen trial batches of fast disintegrating tablets were prepared in order to select the two factors and their level. On the basis of results of preliminary trial batches, the amount of crospovidone were selected as super disintegrating agent.

4. Results of Pre-compression study suggest that an excellent content uniformity was observed because of improvement in flow properties of drugs.

5. Tablets prepared by direct compression methods were found to be good without any sticking, picking, capping and chipping. In Post-compression characterization, drug content was found to be in the range of 95 to 99% with round shape and having hardness of 4- 5 Kg/cm2. Percent weight variation was observed between 4.0 and 6.1 with friability of between 0.40 and 0.59 %.

6. The disintegration time of tablets of drugs prepared by direct compression were found to be in the range of 30-40 seconds.

7. Tablets prepared with highest percentage of Crospovidone i.e. F15 showed the best result. Results of dissolution study showed that more than 50% of the drug was released within the first 5 minutes. More release rate of tablets is accepted for drugs that are required to be released within 15 minutes. Results of Crospovidone showed very more percentage of drug released. This indicates highly porous nature of the prepared fast dissolving tablet which suggested the rapid penetration of water that resulted in rapid wetting, disintegration, and dissolution within the oral cavity.

8. Release kinetic study of developed fast dissolving tablets showed that the mechanism of drug release was first order.

9. Results of stability studies indicated that various test parameters for tablet formulations remain unchanged on storage for three months, indicating stability for up to three months.

10. The results also demonstrated the utility of fast disintegrating tablets formulations in enhancing the solubility and dissolution rate of sparingly soluble drugs.

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