Formulation and Evaluation of Fast Disintegrating Tablets of Tiotropium Bromide and Cetirizine Hydrochloride
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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 enclosed, but conjointly orally disintegrating tablets that are indented to dissolve and/or disintegrate quickly within the mouth.

To fulfill these medical needs, the pharmaceutical technologist have devoted considerable effort to develop a novel type of dosage form for oral administration, the Fast Dissolving Tablet (FDT), tablet that disintegrates and dissolves rapidly in saliva without need of water. The fast dissolving tablets usually dissolve in oral cavity within 15 to 60 s. The faster the drug goes into solution, the quicker the absorption and onset of clinical effects. The development of fast dissolving tablets also provides line extension in the market place (Seager et al., 1998).

USFDA defines FDT as 'A solid dosage form containing medicinal substance or active ingredient which disintegrates and dissolves rapidly usually within a matter of seconds when placed upon the tongue' the disintegration time ranging from several seconds to about a minute.

It can be achieved by different available techniques like direct

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 toleratred. 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
compensation, wet granulation, compression moulding, volatilization, vacuum drying and freeze-drying. They involve different mechanisms like use of high amounts of hydrophilic disintegrating agents of effervescent combinations, which allow the dosage forms to disintegrate quickly in the patient's mouth on contact with saliva (Sanjay et al. 2002). There are more than fifteen fast dissolving products in the market worldwide. This tablet contains agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed as fast disintegrating tablets, as it requires maximum 60 secs to completely disintegrate the tablet (Porter et al., 2001).

Asthma is a common chronic disorder of the airways that involves a complex interaction of airflow obstruction, bronchial hyperresponsiveness and an underlying inflammation (Centers for Disease Control and Prevention [CDC], 2009). A report suggested that, it is estimated that a total of 22 million individuals suffer from asthma, with nearly 6 million of these individuals being children (National Institutes of Health [NIH], 2005).

It affects about 300 million people worldwide and is projected to increase to 400 million by 2025 (Masoli et al., 2004). Medications to treat asthma can be classified as controllers or relievers. Controllers are medications taken daily on a long-term basis to keep asthma under clinical control chiefly through their anti-inflammatory effects. They include inhaled and systemic glucocorticosteroids, leukotriene modifiers, long acting inhaled β2-agonists in combination with inhaled glucocorticosteroids, sustained-release theophylline, cromones, and anti-IgE.

Tiotropium bromide is a novel potent and long-lasting muscarinic antagonist that has been developed for the treatment of chronic obstructive airways disease (COPD). In vitro tiotropium bromide has a potent inhibitory effect against cholinergic nerve-induced contraction of guinea-pig and human airways, that has a slower onset than atropine or ipratropium bromide. After washout, however, tiotropium bromide dissociates extremely slowly compared with the dissociation of atropine and ipratropium bromide. Furthermore, it protects against cholinergic broncho constriction for > 24 h. This suggests that tiotropium bromide will be a useful bronchodilator, particularly in patients with COPD, and may be suitable for daily dosing (Barnes et al., 1995).

Its insolubility in water and blend taste makes it an ideal candidate for fast disintegrating tablets with regards to palatability. Since asthma patients have to strictly follow the dosage regimen for preventing sub therapeutic 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 used to treat concomitant conditions (e.g., allergic rhinitis) without concern that it will interfere with the bronchodilatory effect of albuterol or cause worsening of asthma by itself.

Hence in the present work attempt will be made to develop and evaluate fast disintegrating formulation of tiotropium bromide and cetirizine hydrochloride.

**MATERIALS AND METHODS**

**Materials**

Tiotropium bromide was obtained as a gift sample from Jai Radhe Sales, Ellis Bridge, Ahmedabad, India. Cetirizine hydrochloride was purchased from Himedia Laboratories Pvt. Ltd., Mumbai, India. Talc, Sodium starch glycollate, Crosspovidone,and Magnesium stearate was procured from Loba chemicals Pvt.Ltd. Mumbai, India. Microcrystalline cellulose was purchased from Yarrow chem. Products, Mumbai, India.

**Methods**

**Preparation of fast disintegrating tablets**

Fast disintegrating tablets were prepared by direct compression method because of their several advantages:

- Easiest way to manufacture tablets.
- High doses can be accommodated.
- Use of conventional equipment.
- Use of commonly available excipients.
- Limited number of processing steps.

The fast dissolving tablets were prepared with coprocessed superdisintegrants (Ac-di-sol with crosspovidone and sodium starch glycollate with crosspovidone) and evaluated for pre and post-compression properties. The evaluated parameters were compared with the tablets prepared by physical mixture of superdisintegrants.

The tablets were prepared by using single punch tablet machine (Cadmach, Ahemdabad) to produce flat faced tablets weighing 128 mg each with a diameter of 5 mm. A minimum of 50 tablets were prepared for each batch. Before compression tablet blends were evaluated for mass-volume relationship (bulk density, tapped density, Hausner's ratio, compressibility index) and flow properties (angle of repose). The formulations were developed by using different techniques.

**Technology Followed – Superdisintegrant Addition**

The superdisintegrants (Ac-di-sol, sodium starch glycollate 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).
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.

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

The bulk density ($\rho_b$) 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:

$$\rho_b = \frac{M}{V_b}$$

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

The tapped density ($\rho_t$) 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 ($V_t$)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

$$\rho_t = \frac{M}{V_t}$$

**Angle of repose**

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:

$$\tan \theta = \frac{h}{r}$$

where,

$\theta$ = 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's index)

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)

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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/cm².

**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:

\[
\% \text{ Friability} = \left(\frac{W_i - W_f}{W_i}\right) \times 100
\]

Where,

- \( W_i \) = initial weight of tablets
- \( W_f \) = 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 ± 2°C. 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-Elmer) 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, Crosopovidone 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/cm².

**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 Pharmacopeia. 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 ± 0.5°C 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
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 °C 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.

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°C and 75 ± 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°C and 75 ±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.

REFERENCES


