FORMULATION AND EVALUTION OF CARBIMAZOLE ORAL DISPERSIBLE TABLETS

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ABSTRACT

Carbimazole is used to treat hyperthyroidism. Carbimazole is a pro-drug as after absorption it is converted to the active form, methimazole. Methimazole prevents thyroid peroxidase enzyme from iodinating and coupling the tyrosine residues on thyroglobulin, hence reducing the production of the thyroid hormones T3 and T4. In the present work, an attempt has been made to develop oral dispersible tablets of Carbimazole. Novel method of co processed super disintegrating technology was employed to formulate the tablets. All the formulations were prepared by direct compression method. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good compression parameters and they passed all the quality control evaluation parameters as per LP limits Among all the formulations CBZL5 formulation showed maximum drug release i.e., 97.26% in 10 min hence it is considered as optimized formulation. The CBZL5 formulation contains CP1 as super disintegrate in the concentration of 125 mg. (CP2 contains SSG and CP in 1:2 ratio).

Key words: Oro dispersable, Drug delivery system , Carbimazole , Coprocessed,Super disintegrating technology.

INTRODUCTION

Oral delivery of drugs is by far the most preferred route of drug delivery due to ease of administration, patient compliance and flexibility in formulation. The design of oral controlled drug delivery systems (DDS) is primarily aimed to achieve more predictable and increased bioavailability. Gastric emptying time in humans, which is normally 2-3 hours through the main absorption area (stomach or upper part of intestine), can result in incomplete drug release from DDS leading to diminished efficacy of administered dose. Drug that are easily absorbed from the gastro-intestinal tract (GIT) and having a short half-life are eliminated quickly from the blood circulation. To avoid this problem, the oral controlled release formulations have been developed, as these will release the drug slowly into the GIT and maintain a constant drug concentration in the serum for a longer period of time, one of the feasible approaches to control the gastric residence time (GRT). Orally disintegrating tablets offer an advantage for populations who have difficulty in swallowing (Dysphagia). ODTs are useful among all age groups and more specific with paediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications.

Orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapid melts. However, of all the above terms, United States Pharmacopoeia (USP) approved these dosage forms as ODTs. Recently ODT terminology has been approved by United States Pharmacopoeia, British Pharmacopoeia. Recently, European

Pharmacopoeia has used the term orodispersible tablet for those tablets which disperses readily and within 3 min in mouth before swallowing. Such a tablet disintegrates into smaller granules or melts in the mouth from a hard solid to a gel-like structure, allowing easy swallowing by patients.

Significance of Oro-dispersible tablets:

As ODTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, small packaging size, and ease of handling by patients. No risk of obstruction of dosage form as rapidly dissolves in saliva. Administration without water, anywhere and anytime, hence beneficial for traveling patients who do not have access to water. Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action. Medication as "bitter pill" has changed by excellent mouth feel property produced by the use of flavours and sweeteners in ODTs. Suitable for delivering relatively low molecular weight and highly permeable drugs. Requires minimum number of ingredients and so it is cost effective dosage form.

Challenges in development of ODTs:

1. **Palatability:** It is a formidable challenge for formulation scientists to mask the taste of bitter tasting drugs selected for ODT. As most drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste masked form. Hence, taste masking of the drugs become critical to patient compliance.
2. **Mechanical strength:** In order to allow ODTs to disintegrate in the oral cavity, they are made of either very porous or soft-moulded matrices or compressed in to tablets with very low compression force, which makes the tablets friable or brittle, and difficult to handle. Only few technologies can produce tablets that are sufficiently hard and durable to allow them to be packaged in multi dose bottles, such as Wow tab by Yamanouchi Shaklee, and Durasolv by CIMA labs.
3. **Hygroscopicity /moisture sensitivity:** Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and 5 humidity. Hence, they need protection from humidity which calls for specialized product packaging.
4. **Aqueous solubility:** Water-soluble drugs pose various formulation difficulties because they form eutectic mixture, which result in freezing point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse can be prevented by using matrix-forming excipients such as mannitol that can induce Crystallinity and hence, impart rigidity to the amorphous composite.
5. **Size of tablet:** The degree of ease when taking a tablet depends on the size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.

Tablet Design and Manufacturing Process

Compression Force: The tablet's hardness is influenced by the compression force used during manufacturing. For ODTs, the tablet

must be sufficiently strong to survive andling but not so hard that it resists rapid disintegration in the mouth.

Granulation Method: Wet granulation, dry granulation, or direct compression method are used depending on the properties of the API and excipients. Wet granulation can provide better content uniformity, while direct compression is more efficient and suitable for sensitive APIs.

Porosity and Particle Size: Tablets with higher porosity tend to disintegrate more quickly, improving the rate of dissolution. The particle size of both the API and excipients must be controlled to ensure uniformity and ease of compression.

Disintegration and Dissolution

Disintegration Time: ODTs must break apart quickly when placed in the mouth (typically within 30 seconds), so the formulation must facilitate rapid disintegration.

Dissolution Rate: After disintegration, the API must dissolve quickly to be absorbed effectively. The choice of excipients and the porosity of the tablet influence the dissolution rate**.**

Moisture Sensitivity

Hygroscopicity: Some APIs and excipients are sensitive to moisture, which can cause premature disintegration or degradation of the drug. Moisture-resistant packaging is crucial to maintaining the integrity of ODTs.

Packaging: ODTs are often packaged in blister packs to protect them from humidity and moisture during storage and handling.

Taste Masking

Taste-Masking Technologies: For APIs with a bitter taste, taste-masking methods such as coating the particles, using cyclodextrin complexes, or employing granulation techniques are essential to make the tablet more palatable.

Flavouring: Sweeteners and flavouring agents (e.g., mint, fruit Flavors) are often added to mask any residual bitterness or undesirable taste.

Patient Compliance

Convenience: ODTs offer the advantage of being taken without water, which can be beneficial for patients who have difficulty swallowing traditional tablets or for those who need medication on the go.

PRECAUTIONS Dosage Flexibility: Some ODT formulations may allow for easy division or dosing adjustments, depending on the patient's requirements.

Special precautions has to be taken, that Carbimazole should be used with caution in patients with mild-moderate hepatic insufficiency. If abnormal liver function is discovered, the treatment should be stopped. The half-life may be prolonged due to the liver disorder. Carbimazole should be stopped temporarily at the time of administration of radio-iodine.

DOSE AND METHOD OF ADMINISTRATION:

Carbimazole should only be administered if hyperthyroidism has been confirmed by laboratory tests.

Adults, Initial dosage it is customary to begin carbimazole therapy with a dosage

that will fairly quickly control the thyrotoxicosis and render the patient euthyroid, and later to reduce this. The usual initial dosage for adults is 60 mg per day given in divided doses.

Table:1 Dose for age

Mild cases	20mg
Moderate cases	40mg
Severe cases	40-60mg

The initial dose should be titrated against thyroid function until the patient is euthyroid in order to reduce the risk of over-treatment and resultant hypothyroidism.

Advantages of carbimazole: -

Their cost is lowest of all the dosage forms.

They are in general the easiest and cheapest to package and ship of all oral dosage forms.

Disadvantages of the carbimazole:

Some drugs resist compression in to dense particles, owing to their amorphous nature or flocculent, low density character.

Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, optimum absorption high in the GIT or any combination of these features are very challenging for the formulators.

Thyroid:

The thyroid is a butterfly-shaped endocrine gland located in the front of the neck, just below the larynx (Adam's apple). It produces hormones that regulate metabolism, growth, and development. Thyroid diseases occur when the thyroid gland produces either too much or too little hormone. The thyroid produces thyroxine (T4) and triiodothyronine (T3), which are essential for various body functions**.**

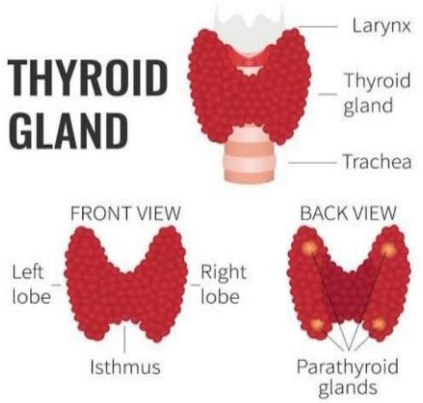

Fig:1 Thyroid gland

Route of administration

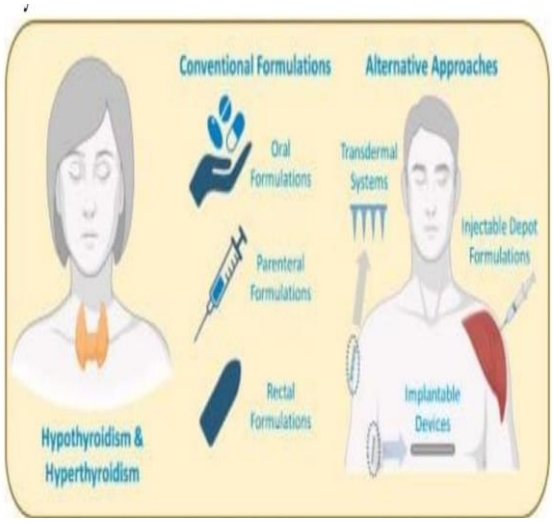

Fig:2 Route of administration

Types of thyroid

Hypothyroidism

Hyperthyroidism

Hypothyroidism (underactive thyroid disease) is a condition that happens when your thyroid gland doesn't make or release enough hormone into your bloodstream. As

a result, your metabolism slows down. This can cause unintentional weight gain and make you feel exhausted all the time. Although weight gain and fatigue aren't specific to hypothyroidism, a simple blood test can help your healthcare provider check for this condition. In general, 18 hypothyroidism is very treatable. Most people can manage the condition with medication and regular follow-up visits with their endocrinologist.

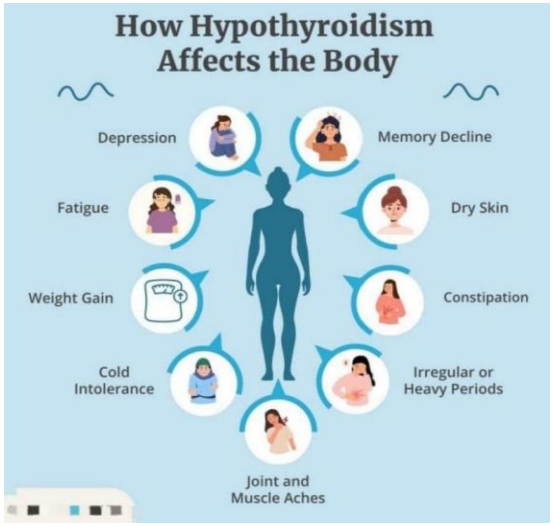

Fig:3 Affect of Hypothyroidism

Hyperthyroidism, also called overactive thyroid, is a condition where your thyroid makes and releases high levels of thyroid hormone. It has multiple possible causes. The main thyroid hormones are triiodothyronine (T3), thyroxine (T4) and thyroid stimulating hormone (TSH). Hyperthyroidism speeds up your metabolism, which can affect several aspects of your health. The condition can throw your whole well-being off balance. You may not feel like yourself or even feel out of control of your body.

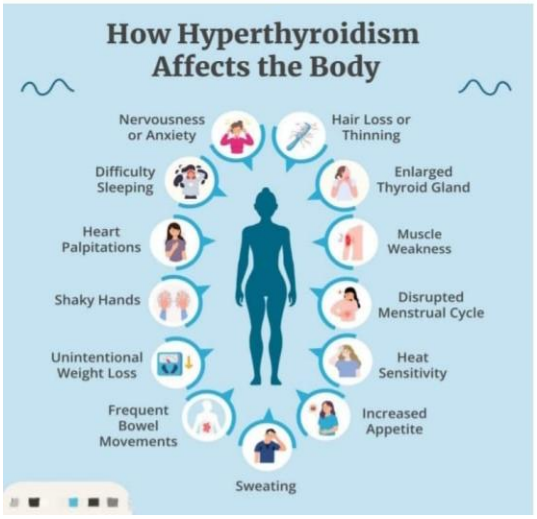

Fig:4 Affect of Hyperthyroidism

Materials

Table:2 Ingredients

Materials	**ty**
Carbimazole	
Sodium starch glycolate&CP	ıt ratios
Magnesium streate	
Talc	

Methodology

Procedure for plotting calibration curve:

For plotting of calibration curve, in a series of 10ml volumetric flasks, 1ml, 2ml, 3ml, 4ml and 5ml of working stock solution (100µg/ml) was pipetted out separately. The volume was made upto the mark using methanol: distilled water (30:70) to get 10µg/ml, 20 µg/ml, 30µg/ml, 40µg/ml, 50µg/ml respectively.

Direct Compression:

Tablet manufacturing with direct compression requires only two operation steps; powder mixing and tableting. The

main advantages of direct compression of tablets is reduced production time and hence reduced production cost. Other advantages include fewer excipients needed, faster dissolution of a drug and fewer stability problems regarding APIs that are heat- or moisture sensitive.

Effect of pH on swelling capacity of super disintegrants

Swelling capacity or (swelling index) according to B.P. 2010 is the volume in millilitres occupied by 1 gram of a drug, including any adhering mucilage, after it has swollen in an aqueous liquid for 4 hours. One gram of each super disintegrant was placed in dry cylinder fixed in water bath. Acidic solution (0.1 N HCl) or phosphate buffer (pH 6.8) was added gradually to these dry samples separately with continuous stirring until the volume completed to 100 ml. The samples were incubated at 370 C for 4 hours. The volume of each super disintegrant was recorded before the addition of the medium and at the end of the incubation time.

Formulation of Orodispersible Tablet

Formulation of Placebo Orodispersible

Tablets (without CMZ) Different placebo formulas (without CMZ) were prepared and tested to obtain the optimum formula that shows the fastest disintegration time in the mouth (in vivo) with good flowability and compressibility of powder blend and accepted hardness and friability of prepared tablets. All the ingredients were passed through mesh No.60. All formulas were prepared using direct compression technique. Each formula was formulated by mixing (geometric mixing) all the ingredients (except the lubricant) for 15 min after which the lubricant was added and blended for another 1minute. The final mixture was compressed using a round bevelled edge double punch, Korsch, tablet machine with a 9 mm flat punch.

Pre-formulation Studies

The goals of the pre-formulation study are: To establish the necessary physicochemical characteristics of a new drug substance, To determine its kinetic release rate profile. To establish its compatibility with different excipients. Determination of absorption maximum (max): Absorption maximum is the wavelength at which maximum absorption takes place. For accurate analytical work, it is important to determine the absorption maxima of the substance under study. Carbimazole was weighed accurately 10 mg and transferred to 100 ml volumetric flask, dissolved in phosphate buffer pH 6.8 and the final volume was made up to 100 ml with phosphate buffer pH 6.8 to get a stock solution (100µg/ml). From the stock solution, 1 ml was pipette out in 10 ml volumetric flask and the final volume was made up to 10 ml with phosphate buffer PH 6.8 to get 10µg/ml. Then this solution was scanned at 200-400nm in UV-Visible double beam spectrophotometer (UV-3200, Labindia, India) to get the absorption maximum (lambda max).

Construction of Carbimazole calibration curve with phosphate buffer pH 6.8:

100mg of Carbimazole was dissolved in 100ml of phosphate buffer pH 6.8 to give a concentration of 1mg/ml (1000µgm/ml). From the above standard solution (1000µgm/ml). 10 ml was taken and diluted

to 100ml with phosphate buffer pH 6.8 to give a concentration of (100µgm/ml). From this stock solution aliquots of 0.2,0.4,0.6,0.8 and 1ml were pipette out in 10ml volumetric flask and the volume was made up to the mark with phosphate buffer PH 6.8 to produce concentration of 2,4,6,8 and(10µgm/ml). respectively. The absorbance (abs) of each conc. was measured at respective (lambda max) i.e., 290 nm.

Drug- excipient compatibility studies by FT-IR:

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany (Alpha T). The potassium bromide pellets were prepared on KBr press by grounding the solid powder sample with 100 times the quantity of KBr in a mortar. The finely grounded powder was then introduced into a stainless-steel die and was compressed between polished steel anvils at a pressure of about 8t/in2 . The spectra were recorded over the wave number of 8000 to dot 400cm-1

Flow properties:

Angle of Repose: The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane.

Bulk Density (BD): Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3.

Tapped density (TD): After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2.

Carr's Index: The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities.

Hausner's ratio: The Hausner ratio is a number that is correlated to the flowability of a powder or granular material.

Formulation of Oral dispersible tablets of Carbimazole:

Preparation of co processed super disintegrates: Co processed super disintegrates were prepared by using sodium SSG and CP. The super disintegrates were mixed in different concentrations and labelled as CP1, CP2, CP3. The blend of super disintegrates was mixed thoroughly for a period of 15 min, collected and used for preparing formulations in different concentrations.

Composition of co -processed super disintegrates CP = co-process super disintegrates

Table:3 Composition of various tablet formulations

Ingredients	CBZ L1	CB ZL2	CBZ L3	CBZ L4	CBZ L5	CBZ L6	CBZ L7	CBZ L8	CBZ L9
Carbimazole (mg)	20	20	20	20	20	20	20	20	20
CP1 (mg)	20	30	40	-	-	-	-	-	-
CP2 (mg)	-	-	-	20	30	40	-	-	-
CP3(mg)	-	-	-	-	-	-	20	30	40
Magnesium Stearate (mg)	3	3	3	3	3	3	3	3	3
Talc(mg)	3	3	3	3	3	3	3	3	3
MCC (mg)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Total (mg)	80	80	80	80	80	80	80	80	80

Post Compression Parameters

Evaluation of uncoated tablets:

Shape and colour: The tablets were examined under a lens for the shape of the tablet and colour by keeping the tablets in light.

Uniformity of thickness: Randomly 10 tablets were taken from formulation batch and their thickness (mm) was measured using a Vernier callipers.

Hardness test: Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness.

Friability test: It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche friabilator (Lab India, FT 1020). It is expressed in percentage (%). Ten tablets were initially weighed [W(initial)] and transferred into friabilator.

Weight variation test: The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The % deviation in weight variation .

Drug Content estimation: The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. Four tablets were weighed and crushed in the mortar. The powder equivalent to 1.25 mg of the drug were weighed and dissolved in 100ml phosphate buffer pH 6.8 to give a concentration of 12.5 µg/ml. 2ml of this solution was taken and diluted to 10ml to give a concentration of 2.5µg/ml.

***In-vitro* dissolution studies:** In-vitro release studies were carried out using a modified USP XXIII dissolution test apparatus (Lab India, DS-800). The dissolution fluid was 500ml of phosphate buffer pH 6.8 at a speed of 50rpm at a temperature of 37°c were used in each test [17]. Samples of dissolution medium (5ml) were withdrawn for every 5min and assayed for Carbimazole by measuring absorbance at 290 nm. For all the tests 5ml of the test medium were collected at specified time intervals and replaced with same volume of phosphate buffer pH 6.8.

RESULT AND DISCUSSION

Standard calibration curve of carbimazole

Table:4 Composition and absorbances obtained for calibration curve of carbimazole in pH 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
0.2	0.175
0.4	0.341
0.6	0.563
0.8	0.682
1	0.899

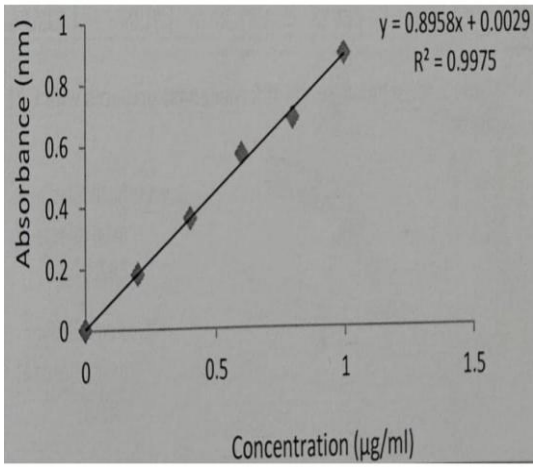

Fig:5 Standard graph of carbimazole in pH 6.8 phosphate buffer

Procedure for plotting calibration curve: For plotting of calibration curve, in a series of 10ml volumetric flasks, 1ml, 2ml, 3ml, 4ml and 5ml of working stock solution (100µg/ml) was pipetted out separately. The volume was made upto the mark using methanol: distilled water (30:70) to get 10µg/ml, 20 µg/ml, 30µg/ml, 40µg/ml, 50µg/ml respectively

Evaluation parameters for oral dispersible tablets of carbimazole

Pre-compression parameters

Table: 5 Pre-compression parameters

Formulation	Bulk density (gm/cm²)	Tap Density (gm/cm²)	Carr's Index (%)	Hausner ratio	Angle of repose (Ø)
CBZL1	0.47	0.57	16.03	1.05	24.02
CBZL2	0.46	0.56	17.22	1.12	23.16
CBZL3	0.46	0.54	17.11	1.14	24.53
CBZL4	0.47	0.55	18.51	1.19	21.08
CBZL5	0.47	0.56	17.36	1.13	22.16
CBZL6	0.51	0.54	17.71	1.15	22.14
CBZL7	0.48	0.57	16.15	1.14	24.12
CBZL8	0.51	0.58	16.09	1.12	23.05
CBZL9	0.49	0.51	17.05	1.11	22.78

Post compression parameters

Table:6 Post compression parameters

Formulation code	Weight Variation (mg)	Hardness (kg/cm²)	Thickness (mm)	Disintegration Time (sec)	Friability (%)	Assay (%)
CBZL 1	81	2.6	1.06	24.03	0.56	98.21
CBZL 2	82	2.5	1.11	23.34	0.54	99.46
CBZL 3	79	2.2	1.08	22.49	0.52	97.37
CBZL 4	81	2.5	1.11	24.91	0.51	97.15
CBZL 5	80	2.7	1.12	23.72	0.54	98.59
CBZL 6	82	2.5	1.11	25.93	0.53	98.67
CBZL 7	81	2.4	1.13	26.54	0.55	99.71
CBZL 8	82	2.7	1.11	24.71	0.56	99.65
CBZL 9	83	2.6	1.12	22.19	0.51	97.81

In-vitro Dissolution studies

Table:7 In-vitro dissolution studies of all formulation

Time (mg)	% drug release of CBZL 1	% drug release of CBZL 2	% drug release of CBZL 3	% drug release of CBZL 4	% drug release of CBZL 5	% drug release of CBZL 6	% drug release of CBZL 7	% drug release of CBZL 8	% drug release of CBZL 9
0	0	0	0	0	0	0	0	0	0
2	24.25	23.19	24.19	23.45	26.77	26.67	21.45	22.52	21.32
4	48.06	37.11	39.25	41.41	51.44	41.51	44.51	37.76	44.41
6	64.41	62.74	74.41	65.16	75.65	72.42	62.74	54.71	64.88
8	83.52	74.45	86.73	82.71	94.71	84.11	77.91	66.56	81.71
10	89.71	80.63	89.51	86.18	97.26	91.09	82.63	81.11	90.15

Compatibility studies

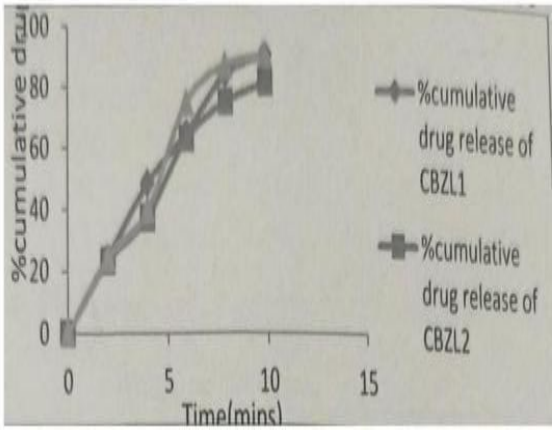

Fig:6 Dissolution profile of formulations prepared with CP1

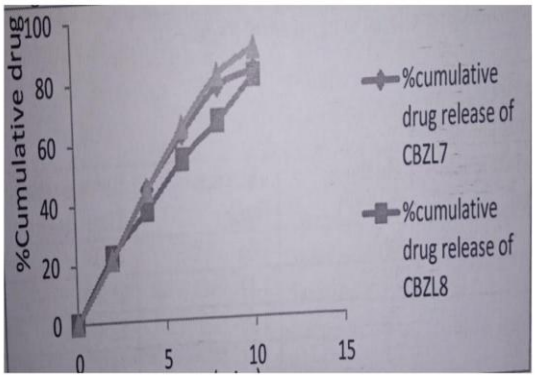

Fig :7 Dissolution profile of formulations prepared with CP2

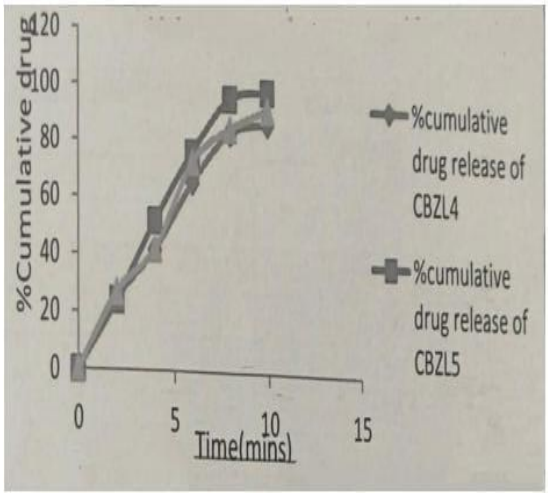

Fig :8Dissolution profile of formulations prepared with CP3

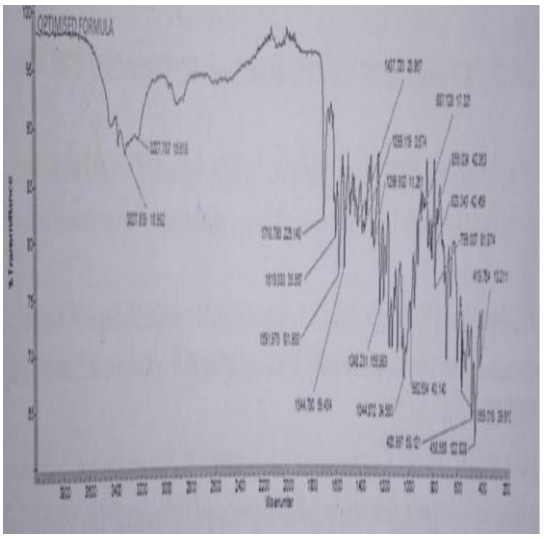

Fig :9 FTIR spectrum of pure drugs

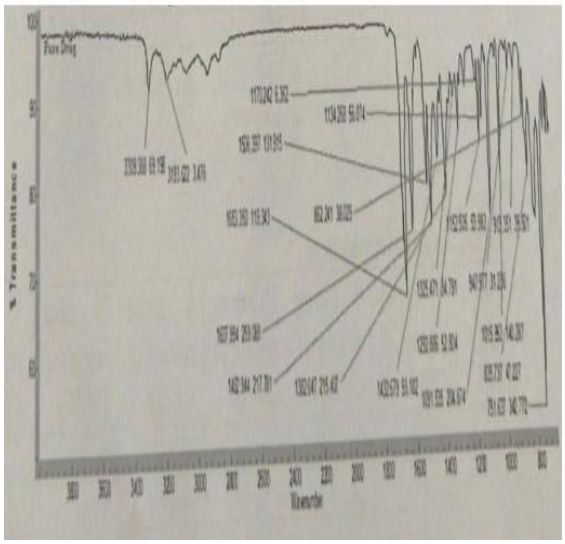

Fig :10 FTIR spectrum of optimized formulation

CONCLUSION

Oral Dispersible Tablets (ODTs) have emerged as an innovative and patient-centric dosage form in modern pharmaceutical development. Their ability to disintegrate rapidly in the mouth without the need for water addresses a significant need among specific patient groups, particularly paediatric, geriatric, and mentally ill individuals who may have difficulty swallowing conventional tablets or capsules (a condition known as dysphagia). This enhances not only patient compliance but also the overall therapeutic efficacy of the medication. From a pharmacokinetic perspective, ODTs can facilitate quicker onset of action by promoting faster dissolution and absorption in the oral cavity and upper gastrointestinal tract. This characteristic is especially advantageous for drugs that require rapid action, such as analgesics, antiemetics, and antihistamines. The development of ODTs, however, presents unique formulation challenges. Critical factors such as taste masking, mechanical strength, mouthfeel, and stability must be carefully balanced. The drug and excipient must be compatible, and the tablet must remain intact during handling and packaging, while still disintegrating quickly upon administration. Recent advancements in excipients—such as superdisintegrants, effervescent agents, and novel polymers—along with innovative manufacturing techniques like lyophilization, direct compression, and sublimation, have helped overcome many of these hurdles. Additionally, regulatory bodies like the FDA and EMA have provided guidelines specific to ODTs, ensuring their quality, safety, and efficacy, which has further encouraged their adoption in the pharmaceutical industry. Emerging studies have also shed light on potential pharmacogenomic influences on Carbimazole metabolism and adverse effect susceptibility. This highlights the growing relevance of personalized medicine in optimizing treatment outcomes and minimizing harm.

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