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Original article

Fast Dissolving Tablets of Carvedilol Using Solvent Evaporation Method

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ABSTRACT:
Fast dissolving tablets are novel type dosage forms for oral administration. Oral route of administration has wide acceptance up to 50 to 60% of total dosage forms. Mainly solid dosage forms are popular because of ease administration, self-medication, pain avoidance as compared to parental and cheap. Carvedilol is a nonselective β- blocker useful in the treatment of hypertension. Carvedilol is poorly soluble in aqueous media. Being a class -II drug, it exhibits low solubility and high permeability. Due to its low solubility characteristics, dissolution is the rate limiting step in drug absorption present work involves attempts to improve dissolution rate through formulation of FDT of Carvedilol. The main advantage of fast dissolving tablets is rapid absorption and thus improved bioavailability and faster on set of action. The super disintegrant used for the preparation of fast dissolving tablets are (crosscarmellose sodium)showed better results when added in the form of drug super disintegrant dispersion prepared by solvent evaporation when compared to direct addition to the formulation in wet granulation. Carvedilol fast dissolving tablet prepared by using dispersion which added 100% intragranularly showed rapid dissolution rate and 100% of drug was released in 30 min. Dissolution profile of pure drug in 0.1 N HCl shows only 79.6% drug release in 2hrs. F4 formulation by wet granulation, results showed that 91.11% was released in 1hr. Evaluation procedures were also done based on the Indian pharmacopeia limits (Friability, Hardness, Disintegration time, Content uniformity, Dissolution rate test) Few high performance liquid chromatographic methods (HPLC) for determination of carvedilol in rat and human plasma has been reported earlier and there is no UV spectrophotometric method for carvedilol in literature. The release kinetics studies shows in first order for all formulations.

Keywords: Carvedilol, Solvent Evaporation, Super disintegrant, Wet granulation.

1. INTRODUCTION

Oral route of administration has wide acceptance up to 50-60% of total dosage forms. Mainly solid dosage forms are popular because of ease of administration, self-medication, pain avoidance as compared to parenteral and cheap [1].

Difficulty in swallowing (DYSPHAGIA) is most common problem of all age groups. Incomplete development of muscular and nervous system in adults and elderly patients suffer from dysphagia, Parkinson's disorders and tremors. it is estimated that 50% of the population is affected by this problem which results in a high incidence of noncompliance and ineffective therapy [2].

The demand for the solid dosage forms that can be dissolved and suspended in water chewed (or) rapidly dissolved in the mouth is particularly strong in the paediatric and geriatric markets with further application to other patients who prefer the convenience of readily administrate dosage form [3].

Development of fast dissolving tablets also provides opportunity for a line extension in the market place. Wide range of drugs (eg neuroleptics, cardiovascular drugs, analgesic, antihistamines, and drugs for erectile dysfunction) can be considered as suitable candidates for this kind of dosage forms.

Appropriate disintegrants which maximize porous structure of matrix and highly hydrophilic excipients are main ingredients of fast dissolving tablets.

Theses dosage forms are placed in the mouth, allowed to disperse and dissolved in the saliva in 15 to 60 sec and then swallowed in the normal way, without need of water which offers fast absorption and onset of the action. The bioavailability of drug from fast dissolving formulation s may be even greater than that observed for standard dosage forms. Furthermore, the side effects may be reduced if they are caused by first pass metabolites [4].

Less frequently they are designed to be absorbed through buccal and small oesophageal mucosa as the saliva passes into the stomach.

Their growing importance was underlined recently when European pharmacopeia adopted the term "Oral dispersible

tablets" as a tablet to be placed in the mouth where it disperses rapidly before swallowing.

Advantages of fast dissolving tablets:

The major advantages of fast dissolving tablets formulations is that it combines the advantages of both liquid and conventional tablet formulations, the following are the advantaged of the fast dissolving dosage forms:

•Administration so easy for the patients who cannot swallow such as elderly, stoke victims, and bed ridden patients, patients who should not swallow such as those effected by renal failure and patients who refuses to swallow such as pediatrics geriatric and psychiatric patients [5].

•FDT is convenient to take and thus improve patient compliance, which is critical element in the success of therapy.

•Rapid absorption and thus improved bioavailability and so faster onset of action.

•Formulation is cleared from the oesophagus especially in the supine position without lodging or sticking to it when swallowed, thus offering improved safety.

•Requires no water intake for oral administration of these tablets.

•Any pre gastric absorption avoids first pass metabolism.

•They should allow high drug loading.

Techniques currently used to formulate fast dissolving tablets:

•Tablet molding

•Freeze drying

•Spray drying

•Sublimation

•Disintegration addition

•Use of sugar-based excipients

Tablet Molding:

Fast dissolving tablets can be prepared by moulding technology using water soluble ingredients so that the tablets dissolve completely and rapidly.

In this technology the various ingredients are blended, moisten with hydro alcoholic solvent and molded into tablets at low compression pressure less than conventional dosage form. The solvent is removed by air drying. Molded tablets possess porous structure, which facilitate easy dissolution passing a powder blend through very fine screen increases dissolution rate.

Molded tablets so prepared by above method posses low mechanical strength, which can be increased by adding a binding agent like sucrose, polyvinylpyrrolidine, cellulose polymers to the solvent system

Molded tablets also show poor taste masking characteristics.

In order to overcome the taste problems taste marked active drug particles were used into a lactose based triturate form. The taste masked discrete particle of active ingredients were prepared by subjecting a molten mixture of hydrogenated cotton seed oil, sodiumbicarbonate, lecithin, polyethylene glycol and an active ingredient to spray congealing process .

Recently molded forms are prepared directly from a molten matrix in which drug is dissolved or dispersed or by evaporating the solvent from a drug solution or suspension at standard pressure. The drug can exist as discrete particles or micro particles dispersed in matrix .it can dissolve totally in the molten carrier to form a solid solution or dissolve partially in the molten carrier while the remaining particles stay undissolved and dispersed in the matrix. The characteristics of the tablets (such as disintegration time, drug dissolution rate and mouth feel) will depend on the type of dispersion.

Freeze drying:

Freeze drying and lyophilization can be utilized to prepare mouth dissolving tablets to create an amorphous, porous structure that commonly dissolve rapidly. in addition to rapid dissolution, it also accelerates absorption and increases bioavailability (when compared with conventional compressed tablets). The freeze drying process consists of three phases [6]:

1. Freezing to bring the material below its eutectic zone.
2. Sublimation drying or primary drying to reduce moisture to around 4%W/W of drying product.
3. Desorption or secondary drying to reduce bound moisture to the required final value.

The main advantage being that pharmaceutical substances can be processed at non elevated temperatures thereby eliminating adverse thermal effects and stored in adry state with relatively few shelf life stability problems. More over the lyophilization process imparts a glassy amorphous structure to the bulking agents.

The major disadvantages of the final dosage forms include the lack of physical resistance in standard blister packs and their limited ability to accommodate adequate concentrations of active ingredient.

However, in order to improve stability problems, blank et al used a mixture of mannitol and natural gum as carrier materials in the formulation of freeze dried tablets and concluded that the tablets showed improved stability in blister pack even when they are stored in stressful conditions [3].

Spray drying:

Spray drying can be used for the preparation of rapidly dissolving tablets. The formulations are prepared by using hydrolysed and non-hydrolysed gelatine as supporting agent. The composition contains a bulking agent (mannitol, lactose), a disintegrant (sodium starch glycolate, croscarmellose sodium) and an acidic material (eg citric acid) and /or alkali material (eg sodium bicarbonate) to enhance dissolution and disintegration. The support matrix is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. This is then mixed with the active ingredient and compressed into tablet. The FDT prepared from spray drying technique disintegrates with in 20 sec when immersed in an aqueous medium.

Sublimation:

The basic principle involved in preparing FDT by sublimation technique is addition of volatile salt to the tabletting components, mixing the components to obtain a substantially homogenous mixture and volatilizing the volatile salt.

Compressed tablets that contain a highly water-soluble excipient as a tablet matrix material often do not dissolve rapidly in water. This is because of low porosity of compressed tablets that hinder water penetration into the matrix.

The removal of volatile salt creates porous in the tablet, which help in achieving disintegration when tablet come in the contact with saliva and also exhibit good mechanical strength.

The inert volatile ingredients the volatilize readily (urea, ammonium carbonate, ammonium bi carbonate, hexamethylenetetramine, benzene, camphor) were mixed with other ingredients and compressed into the tablets. Volatile materials were then removed by sublimation which generates porous structure. Additionally, severely solvents e.g., cyclohexane, benzene and tertiary butanol are used as per forming agents.

Steps involved in sublimation:

Use of sugar based excipients:

The high aqueous solubility and sweetness imparted by sugar-based excipients can be used in the formulation of FDT. Sugar based excipients. e.g., sorbitol, mannitol, dextrose, xylitol, fructose, maltose, mannitol starch hydrolysate and polydextrose are Bulking agents. Their high aqueous solubility and sweetness imparts a pleasing mouthfeel and good taste masking, nearly for all formulations of rapidly dissolving tablets [7, 8].

Disintegrant addition:

Addition of disintegrants in fast dissolving tablets lead to quick disintegration of tablets and hence improves dissolution. The basic principle involved in formulating FDT by disintegrant addition technique is addition of super disintegrants in optimum concentration so as to achieve rapid disintegration along with the good feel. Fast disintegration of tablets can also be achieved by incorporating effervescent disintegrating agents which generate CO2.This phenomenon also resulted in partial taste masking of unacceptable taste of the drug.

Drug profile

Carvedilol is a nonselective ß-adrenergic blocking agent with a blocking activity. Carvedilol is chemically designated as (±)-1-(Carbazol-4-yloxy)-3-[[2-(0-methoxyphenoxy) ethyl] aminol-2-propanol [9].

It has the following chemical structure.

Empirical Formula: C24H26N2O4

Molecular weight: 406.5

Appearance:

Carvedilol is an odourless, white to off-white amorphous powder

Solubility:

Carvedilol is freely soluble in dimethyl sulfoxide; soluble in methylene chloride and methanol; sparingly soluble in 95% ethanol and isopropanol; slightly soluble in ethyl ether. Practically insoluble in water gastric fluid (simulated, TS, pH1.1) and intestinal fluid (simulated, TS without pancreatin, pH 7.5) Carvedilol is a base having pka7.86 which is ionized only at low pH (in gastric juice). The partition coefficient of carvedilol in then-octonal/water system is 5.6.

Clinical pharmacology:

Mechanism of action:

Carvedilol is a racemic mixture in which non-selective B-adreno receptor blocking activity is present in S (-) enantiomer anda_1- blocking activity present in both R (+) and S(-) enantiomers atequal potency. It has no intrinsic sympathomimetic activity.

B- Adrenoreceptor blocking activity of Carvedilol

(1) Reduces cardiac output in normal subjects;

(2) Reduces exercise and /or isoproterenol Tachycardia and

(3) Reduces reflex orthostatic tachycardia.

Significant ß-adrenoreceptor blocking effect is usually seenwithin 1 hour of drug administration. The mechanism by which ß-blockade produces antihypertensive effectestablished.

A_1-adrenoreceptor blocking activity of Carvedilol causes

(1) Attenuation of pressor effects of phenylephrine.

(2) Causes vasodilatation.

(3) Reduces peripheral vascular resistance.

These effects contribute to the reduction of blood pressure and usually seen within 30min of drug administration.

Pharmacokinetics

Absorption:

Following oral administration, peak serum levels of Carvedilol are observed within 1 to 1.5 hrs with absolute bioavailability of approximately 25% to 35% due to significant degree of first pass metabolism. Plasma concentrations achieved are proportional tothe oral dose administered.

Distribution:

Carvedilol is more than 98% bound to plasma proteins primarily with albumin. The plasma- protein binding is independent of concentration over the therapeutic range. Steadystate apparent volume of distribution is approximately 115Lindicating substantial distribution into extra vascular tissues.

Metabolism:

Carvedilol is metabolized primarily by aromatic ring oxidation and glucuronidation. The oxidative metabolites are further metabolized by conjugation via glucuronidation and sulfation. The metabolites of carvedilol are excreted primarily via the bile into the feces. Demethylation and hydroxylation at the phenol ring produce three active metabolites with a-receptor blocking activity. Based on preclinical studies, the 4'-hydroxyphenyl metabolite is

approximately 13 times more potent than carvedilol for B-blockade.

Carvedilol undergoes stereo selective first-pass metabolism with plasma levels of R(+)-carvedilol approximately 2 to 3 times higher than S(-)-carvedilol following oral administration in healthy subjects. The mean apparent terminal elimination half-lives for R(+)-carvedilol range from 5 to 9 hours compared with 7 to 11hours for the S(-)-enantiomer.

The primary P450 enzymes responsible for the metabolism of both R(+) and S(-)-carvedilol in human liver microsomes wereCYP2D6 and CYP2C9 and to a lesser extent CYP3A4, 2C19, 1A2,and 2E1. CYP2D6 is thought to be the major enzyme in the 4'- and5'-hydroxylation of carvedilol, with a potential contribution from3A4. CYP2C9 is thought to be of primary importance in the O-methylation pathway of S(-)-carvedilol.

Excretion:

Carvedilol is eliminated predominantly via hepatic metabolism primarily excreted via feces and less than 2% of the dose excreted unchanged in urine.

Plasma clearance ranges from 500- 700ml/min.

The mean elimination half-life (t1/2) for R (+) -carvedilol range from 5-9 hrs compared with 7-11 hrs for S (-)-enantiomer. Compared with healthy adults (24 to 37 yrs. old) the elimination half- life is approximately 50% shorter in paediatric congestive heart failure patients (age 6 weeks to 19 yrs.).Elimination half-life increases with age in paediatric patients. Inpatients less than 3 yrs. old, the half-life was 2.2hrs and inpatients5-19 yrs. old, the half-life was 3.6 hrs.

Dosage and Administration:

Dosage must be Individualized and closely monitored by the Physician. The recommended starting dose is 3.125 mg twice daily for two weeks. If this dose is tolerated, it can then be increased to6.25 mg twice daily. Dosing should then be doubled every 2 weeks to the highest level tolerated by the patient. At initiation of each new dose, patients should be observed for signs of dizziness or light-headedness for one hour. The maximum recommended dose is 25 mg twice daily in patients weighing less than 85 kg (187 lbs)and 50 mg twice daily in patients weighing more than 85 kg in congestive heart failure whereas total daily dose should not exceed50mg in hypertension.

Adverse Effects:

Frequently reported adverse events with carvedilol therapy in clinical trials include dizziness, bradycardia, hypotension, and oedema.

Contraindications:

Carvedilol could not be given to patients with severe hepatic impairment.

Excipient profile

SUPERDISINTEGRANTS

Croscarmellose Sodium (AC -Di-SOL) :

It is cross-linked sodium carboxy methyl cellulose, appears as white to off white and is very free flowing powder. It is insoluble in water, swells only in two dimensions leaving fibre length essentially the same.

Since croscarmellose is the most efficient disintegrating agent,it is postulated that the rate, force, and extent of swelling play an important role.

Croscarmellose sodium occurs as an odourless, white coloured powder. It is chemically cross-linked sodium salt of cellulose, carboxymethyl ether. It is a cross linked polymer of carboxy methylcellulose sodium. It has a molecular weight of 90,000 - 7,00,000and the following structural formula.It is a stable though hygroscopic material and hence it shouldbe stored in a well-closed container in a cool, dry place.

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules. Intablet formulations, it may be used in both direct compression andwet granulation process. When used in wet granulations, it is best added in both the wet and dry stages of the process so that the wetting and swelling ability of the disintegrant is best utilized. Concentrations of up to 5% w/w of it may be used as a tablet disintegrant although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet granulation process. Concentrations of 10-25% w/w of croscarmellose sodium may be used as disintegrant in capsules.

SOLUBILITY:

Completely insoluble in water, acids, alkalis, Swells rapidly inwater. Rapidly disperses in water.

Chemical activity:

It is chemically inert. It has a high adsorptive capacity, forms reversible physical complex with any molecules without the formation of covalent chemical bonds.

Applications:

Used as dissolution aid for tablets, capsules or pellets.

Wet granulation- Disintegrant/super disintegrant.

Dry granulation -It has greatest rate of swelling compared to other disintegrants.

Direct compression-It has greater surface area to volume than other disintegrants typically used at a level of 1 to 3%.

Stability & Storage containers- It is stable though scope material croscarmellose sodium should be stored should be stored in a well closed container in a cool & dry place.

Sodium starch glycolate (**PRIMOJEL**):

It is a white to off white, odorless, tasteless, and free flowing powder. It is chemically, sodium salt of a carboxymethylether of starch. It has a molecular weight of 5,00,000-10,00,000.

It is sparingly soluble in ethanol (95%), practically insoluble in water. At a concentration of 2% w/v it disperses in cold water and settles in the form of a highly hydrated layer. Swell equally in all three dimensions. Used as dissolution aid for tablets, capsules and pellets of tablets and granules non - viscous in nature. In water it swells up to 300 times its volume. Absorbs water rapidly, swells 7-12 folds in less than 30sec. which leads rapid disintegration. It is stable and

should be stored in a well - closed container to protect it from humidity and temperature that may cause caking.

It is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct compression or wet granulation processes. The usual concentration employed in a formulation is between 2-8% with the optimum concentration of about 4% although in many cases, 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.

Crosspovidone (KOLLIDON Cl) :

Cross povidone is a white to creamy- white, finely divided, free flowing practically tasteless, odourless or nearly odourless hygroscopic powder. Cross povidone is chemically 1-ethenyl -2- pyrrolidone homopolymer. It is a water insoluble synthetic cross- linked homopolymer of N-vinyl-2-pyrrolidone. It has a molecular formula of $(C_6H_9NO)N_2$, molecular weight of > 10,00,000 and the following structural formula:

It is practically insoluble in water acids and alkali and most common organic solvents swells rapidly in water. Cross-povidone is used as tablet disintegrant at 2-5% concentration in tablets prepared by direct compression (or) wet and dry granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity with little tendency to gel formation. Swells little but returns to its original boundaries quickly after compression. Wicking or capillary action also is postulated to be major factor in the ability of cross -povidone to function.

Along with these super disintegrants, commonly used disintegrant is low- substituted hydroxyl propyl cellulose.

Low substituted hydrroxy propylcellulose (LHPC)

Description: It is a low - substituted hydroxyl propyl ether of cellulose.

Solubility- It is insoluble in water and alcohol. Swells rapidly in water and forms viscous solution.

It contains not less than 5% and not more than 16% of hydroxyl propyl groups on adriedbasis.

Applications:

L-HPC used as disintegrant in wet granulated and directly compressed tablets. Types with larger average particle size and higher hydroxypropyl content show higher degree of swelling (LH-20, LH-21). Some L-HPC grades (e.g.: L-HPC) provides greater binding while retaining disintegration properties.

2. MATERIALS AND METHODS:

Analytical method for the estimation of carvedilol

Few High-Performance Liquid Chromatography (HPLC)methods for the determination of carvedilol in rat and humanplasma has been reported 20-24 earlier and there is no UVSpectrophotometric method for Carvedilol in Literature.

UV method for the estimation of Carvedilol in the present investigation:

A Spectrophotometric method based on the measurement of absorbance at 243 nm was used in the present study for estimation of carvedilol from the samples. Calibration curve were constructed for the estimation of carvedilol in 0.1 N HCI [10].

Materials:

Carvedilol (Gift Sample from M/s. Micro labs Mumbai) Methanol (Excela R, Qualigens fine chemicals, Mumbai) Hydrochloric acid. (National Chemicals, Hyderabad)

Standard solution:

50 mg of carvedilol was dissolved in methanol in a 50 ml volumetric flask and the solution was made up to the mark with methanol [11].

Procedure:

The standard solution of carvedilol was subsequently diluted with 0.1 N Hydrochloric acid to obtain a series of dilutions containing 1, 2, 3, 4 and 5 ug of carvedilol in 1 ml solution and the absorbance of these solutions was measured at 243 nm in spectrophotometer (UV spectrophotometer) against corresponding blank.

The concentration of Carvedilol and the corresponding absorbance values were given in table 4-. The calibration curve for the estimation of Carvedilol was constructed by plotting linear best fit between the concentration of Carvedilol and the corresponding mean absorbance values. The calibration curve for Carvedilol in 0.1N HCI was shown in fig 2. The value of correlation coefficient, slope(m), intercept [12].

Table 1: Calibration curve for the estimation of carvedilol in 0.1N HCL

S. NO	CONCENTARTION µg/ml	ABSORBANCE
1	0	0
2	1	0.087
3	2	0.168
4	3	0.251
5	4	0.328
6	5	0.435

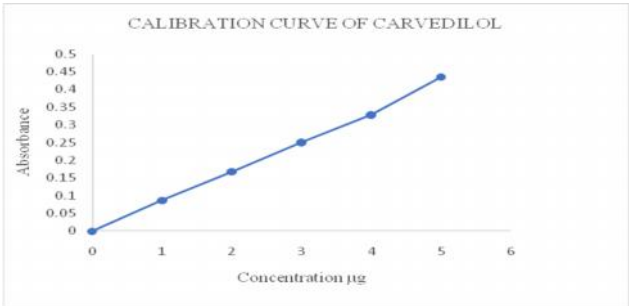

Fig 1: Calibration curve of carvedilol

Table 2: Analytical parameters

S NO	PARMETERS	VALUES
1	Slope	0.0856
2	Intercept	0.003
3	Correlation coefficient®	0.9982
4	Beers law range (µg/ml)	1 to 5
5	%RSD OR % CV	0.486

UV method was found to be accurate and precise (%CV<5). The method obeyed Beer's law in the concentration range of

1- 5 µg/ml. The correlation coefficient was found to be 0.9999, which shows linear relationship between the concentration of carvedilol and absorbance. Thus the method was found to be suitable in the present investigation for the estimation [13].

Materials:

1. Carvedilol (gift sample form Micro labs Mumbai)
2. Potato starch (S.D Fine chem)
3. Croscarmellose sodium (gift sample form Micro labs)
4. Polyvinyl pyrrolidine (S.D Fine chem)
5. Talc (S.D Fine chem)
6. Magnesium stearate (S.D Fine Chem)
7. Lactose (S.D Fine chem)
8. Dichloromethane (Qualigens)
9. Methanol (Lobal Chemi
10. Hydrochloric acid (Qualigens)

Instruments:

1. UV Spectrometer (ELICO SL210)
2. Dissolution rate test equipment
3. USP Standard Disintegration apparatus Electronic Rotary Tableting machine
4. Friability
5. Monsanto hardness tester

Preparation of carvedilol FDT

By wet granulation technique:

Carvedilol tablets are prepared by wet granulation using 1% PVP in alcohol as binder and potato starch, croscarmellose sodium as disintegrants**.**

Table 3: Various formulation of carvedilol tablets.

Materials for 1 tablet (mg)	I	II	III	IV
Carvedilol	25	25	25	25
Potato starch	30	-	-	-
Croscarmellose sodium	-	10	10	10
Talc	4	4	4	4
Magnesium stearate	4	4	4	4
PVP in alcohol	2	2	2	2

Tablet was made up to 200mg with lactose as diluent.

Procedure for Formulation I &II:

Weighed quantities of drug, lactose and 50% disintegrant were taken and made into damp mass using required amount PVP solution and passed through 12 mesh to obtain granules. Wet granules were allowed to dry 60^0c and dried granules were passed through 16mesh.thus obtained granules were bolted with talc, magnesium stearate and remaining 50% of disintegrant and compresses into tablets.

Preparation of dispersion of drug with super disintegrant by solvent evaporation:

Co evaporation (or) dispersion of drug with croscarmellose sodium was prepared by dissolving drug and croscarmellose sodium in dichloromethane separately and taking them into a china dish. Both the solutions were mixed and triturated with pestle for evaporation of solvent and dried for 10 min for complete removal of solvent [14].

In formulation III 50% dispersion was added into granularly and remaining 50% dispersion intergranularly to the formulation.

In Formulation IV, total dispersion was added intragranularly to the formulation.

Evaluation of tablets:

The 4 formulations were evaluated for hardness, friability, content uniformity, and disintegration time and dissolution rate test [15].

Hardness test:

Monsanto hardness tester was used to determine the hardness of tablet.

Friability test:

10 tablets were taken into friabilator, which were weighed initially and rotated for 4 min at 25rpm. At the end of 4min, they were weighed again to get the loss in weight of tablets.

Content uniformity:

Five tablets were taken and powdered from that, sample equivalent to 25mg of drug was taken and transferred into 100ml volumetric flask. Methanol (20ml.) was added and gently heated on water bath to dissolve the drug, cooled to room temperature and volume was made up to mark with methanol. This was filtered. From that filtrate 1ml was taken and diluted with 0.1N HCl and absorbance of this solution was measured as per analytical method [16].

Disintegration test:

By using USP standard apparatus, tablets were tested for disintegration time at 37±0.50c, taking distilled water as medium.

Dissolution Study:

The *in-vitro* drug release studies for all formulations were studied using USP XXI type-1 (Paddle) dissolution rate test apparatus. 900ml of 0.1N HCl solution was used as dissolution medium. The speed of the paddle was set at 50rpm and the temperature of the medium was mentioned at 37±0.50c. 5ml samples were withdrawn at predetermined intervals up to 2hrs and replacements were done with fresh dissolution medium. The samples were suitably diluted and analysed for drug content by UV spectroscopy. For comparsion, dissolution studies of pure carvedilol and commercial carvedilol, tablets were also conducted [17].

Table 4: Evaluation tests for various formulations of carvedilol

Product	Hardness (kg/cm^2)	Friability (%)	Disintegration time (sec)	Drug content (%)
F_1	4.5	0.17	540	90
F_2	4.2	0.5	35	90
F_3	3.8	0.08	15	96
F_4	3.5	0.19	10	98
Commercial product	4.3	0.1	360	100

Table 5: Dissolution profile of carvedilol pure drug

Time (min)	Cumulative % drug released	% Remaining to be released	Log% Remaining to be released
5	30	70	1.85
10	49.2	50.8	1.71
15	53.2	46.8	1.67
30	59.6	40.4	1.60
45	71.6	28.4	1.45
60	72.4	27.5	1.44
90	76.7	23.3	1.37
120	79.6	20.4	1.31

Table 6: Comparative dissolution profiles of pure drug, F_1,F_2,F_3,F_4 and commercial product of carvedilol

Time (min)	Cumulative % drug released					
	Pure drug	F_1	F_2	F_3	F_4	Commercial product
5	35.5	30.93	66.66	80	82.73	34.42
10	49.2	62.53	75.44	85.41	86.73	55.28
15	53.2	69.82	83.55	89.5	97.9	60.85
30	59.6	77.42	96.35	98.95	100	67.71
45	71.6	85.55	100	100	-	75
60	72.4	91.11	-	-	-	80.14
90	76.7	95.55	-	-	-	85.71
120	79.6	100	-	-	-	90

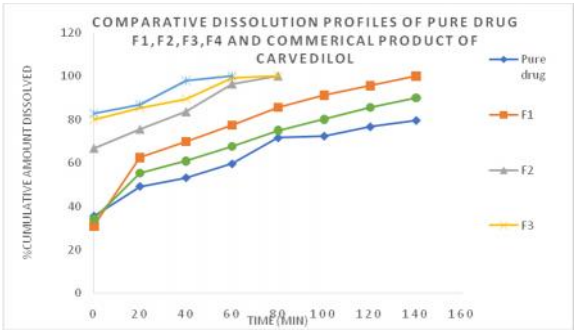

Fig 2: Figure shows comparative dissolution profiles of pure drug, F_1,F_2,F_3,F_4 and commercial product of carvedilol

Table 7: Percent amount remaining to be released from pure drug, F_1,F_2,F_3,F_4 and commercial product of carvedilol

Time (min)	% Amount Remaining to be Released					
	Pure drug	F_1	F_2	F_3	F_4	Commercial product
5	70	61.07	33.34	20	17.27	65.58
10	50.8	37.47	25.56	14.59	13.27	44.72
15	46.8	30.18	16.45	10.5	2.1	39.15
30	40.4	22.58	3.65	1.05	-	32.29
45	28.4	14.45	-	-	-	25
60	27.56	8.89	-	-	-	19.86
90	23.28	4.45	-	-	-	14.29
120	20.4	-	-	-	-	10

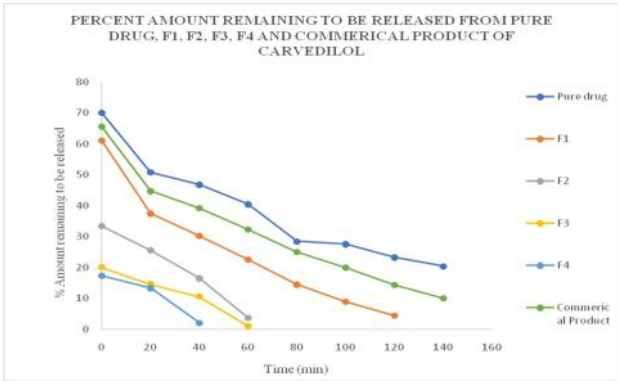

Fig 3: Figure shows percent amount remaining to be released from pure drug, F_1,F_2,F_3,F_4 and commercial product of carvedilol

Table 8: Log % remaining to be released from pure drug, F_1, F_2, F_3, F_4 and commercial product of carvedilol

Time (min)	Log % Remaining to be released for pure drug,F1, F2, F3, F4 and Commercial Product					
	Pure drug	F_1	F_2	F_3	F_4	Commercial product
5	1.85	1.785	1.522	1.3	1.23	1.816
10	1.71	1.573	1.407	1.16	1.12	1.65
15	1.67	1.479	1.216	1.02	0.32	1.592
30	1.6	1.352	0.562	0.02		1.509
45	1.45	1.159				1.397
60	1.44	0.948				1.297
90	1.37	0.648				1.144
120	1.31					1

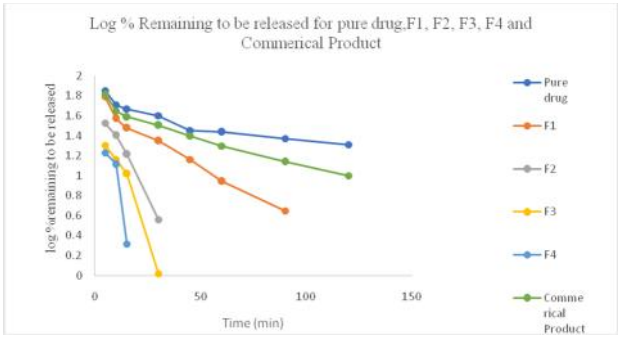

Figure 4: Figure shows log % remaining to be released from pure drug, F_1, F_2, F_3, F_4 and commercial product of carvedilol

Table 9: Dissolution parameters obtained for pure drug, F_1,F_2,F_3,F_4 and commercial product of carvedilol

Product	Release Kinetics						
				First Order		Zero Order	
	DE_{30}	T_{50}	T_{90}	K(min)	r	K(mg/min)	r
Pure drug	59.6	60	9.1	0.0115	0.896	0.017	0.18
F_1	77.4	23.1	3.5	0.03	0.958	0.598	0.775
F_2	96.3	6.7	1	0.103	0.984	0.0005	0.099
F_3	98.9	4.98	0.75	0.139	0.976	0.015	0.27
F_4	100	2.92	0.44	0.23	0.967	0.253	0.698
Commercial product	67.7	40.76	6.5	0.016	0.95	0.544	0.79

PATENTED TECHNOLOGIES OF FD DRUG DELIVERY SYSTEMS:

1. Zydis technology
2. Wave tab technology
3. Orasolv technology
4. Durasolv technology
5. Wow tab technology
6. Fuisz technology
7. Shear form technology
8. Ceform technology

Table 10: Some of the patented technologies

Some of the patented technologies			
Technology	**Trade name**	**Active ingredient**	**Category**
(freeze drying) Claritin	Feldenefast	Piroxicam	Antirneumatic (Non Steroidal)
	Reditab	Loratidine	Antihistamine
	Maxalt MLT	Rizatriptan	Antimigrane
	Zyprexia	Olanzapine	Antipsychotic
	Pepcid RPD	Famotidine	Antinistamine
	Zofran ODT	Ondansetron	5-MTSAntagonist
	Zoming ZMT	Zolmitriptan	Antimigrane
	Zelapar TM	Selegilline	Antipsychotic
2. Wave tab teeh-products Benadryl – Diphenhydarmine. Allergy and Sinus Fast melt technology			
3.Orasolv Texhnology	Remeson (Soltab)	Mirtazepine	Antipyretic
	Tempra first (Tabs)	Acetaminophene	-
4.Durasolv product	Nulevlegeos	Hyoscyamine (Sulfate)	-
	Zoming ZMT	Zolmitriptan	-

Table 11: Commercially available mouth dissolving tablets

Technology	Trade name	Active Ingredient	Category	Manufacturer
Freeze drying	Feldenefast melt	Piroxicam	Antirenumatic Non-steroidal	Pfizer inc,NY,USA
	Claritin redi tab	Loratadine	Antihistamine	Schering.
	Maxalt MLT	Rizatiptan	Antimigraine	Plough corp merck&co, NJ, USA
	Zyprexia	olanzapine	Antipsychotic	Eli lilly, Indianapolis USA
	Pepcid RPD	Famotidine	Antihistamine	Merck&co, NJ, USA
	Zofran-ODT	Ondansetron	5-HT Antagonist	Glaxo wllcome, Middlesex, UK
	Zomig-ZMT	Zolmitriptan	Antimigraine	Astrazeneca,willmin gson USA.
	Zelapar TM	Selegilline	Antipsychotic	Amarin Corp, London
Disintegrant Addational	Tempra quicklets	Acetaminophen	Antipyretic	Bristol-Myers squibb,NY,USA
	febrectol	paracetamol	Antipyretic	Prographarm,chateau neu, France.
	Nimulide MDT	Nimesulide	Antipyretic	Panacea biotech, New Delhi,India
	Torrox MT	Refecoxib	Cox -2 inhibitors ,NSAID	Torrent pharmaceuticals ,Ahmedabad, India
	Olanex instab	olanzapine	Anti psychotic	Ranbaxy labs Ltd., New Delhi,India.
	Romilast	Montelukast	Anti asthamatic	Ranbaxy labs Ltd., New Delhi,India.
Sugar based excipient	Benadryl fast melt	Diphenyl hydramine &pseudoephedrine	Antiallergic	Warner lambert,NJ,USA.

3. RESULTS AND DISCUSSION

Carvedilol is a nonselective β-blocker useful in the treatment of hypertension. Carvedilol is poorly soluble in aqueous media. Being a class – II drug, it exhibits low solubility and high permeability. Due to its low solubility characteristics, dissolution is the rate limiting step in drug absorption, present work involves, attempts to improve dissolution rate through formulation of fast dissolving of carvedilol [18].

The method selected for the preparation of fast dissolving tablet of carvedilol is by using super disintegrant (croscarmellose sodium)

Dissolution profile of pure drug in 0.1 N HCl shows only 79.6% drug release in 2hr.

In the formulation of carvedilol, initially potato starch (15%) and super disintegrant (5%) were added to the formulation by wet granulation technique. Results showed that 91.11% was released in 1 hr in formulation containing 15% potato starch and 100% was released in 45min from thr formulation containing super disintegrant [19].

Then dispersion of drug with super disintegrant was prepared by solvent evaporation. In formulation 3, 50% dispersion was added intragranularly and remaining 50% intragranularly, 1 in formulation 4, all the dispersion was added intragranularly.

Formulation 4 showed rapid drug release profile i.e, it releases 98% drug in 15min whereas formulation 3 release 90% drug.

The formulation 3 and 4 showed greater dissolution efficiency in 30 min (DE 30) viz, 98.9,100%, respectively than formulation 1 and 2 which gave values of 77.4 and 96.3 respectively. All these tablets showed required hardness, limited % friability and good disintegration time (with I.P limits) [20, 21].

All the formulation was evaluated for drug content and results are given in table 6. The percentage drug content was in the range of 90-100%.

4. SUMMARY AND CONCLUSION

Fast dissolving tablets are a novel type of tablet dosage forms for oral administration. These have the advantage of

both solid and liquid dosage form the major conclusion drawn from this work are as follows.

1. Super disintegrant (croscarmellose sodium) showed better results when added in the form of drug super disintegrant dispersion prepared by solvent evaporation when compared to direct addition to the formulation in wet granulation. Carvedilol past dissolving tablet prepared by using dispersion which added 100% of drug was released only in 30min.
2. Drug release profile of fast dissolving tablets followed first order release.
3. Commercial immediate release tablets "Cardivas" showed lower dissolution rates than fast dissolving tablets prepared.

The above discussed results clearly indicated the usefulness of the FDT in the improvement of dissolution rate of poorly soluble drug like carvedilol whose bioavailability is dissolution rate limited [22]. However further studies like infrared spectrophotometric studies to know whether there are any interactions between drugs and super disintegrant, preparation of FDT by other approaches using different excipients, characterization in term of its long term stability and in vivo absorption studies are necessary

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