

Research Article

Formulation and Evaluation of Mouth Dissolving Tablets of Nebivolol HCl for Treatment of Hypertension

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ABSTARCT

Novel drug delivery system and formulation research are oriented towards increasing safety and efficacy of existing drug molecule through novel concepts of drug delivery. As precision of dosing and patient's compliance become important prerequisite for quick relief from Hyper tension, an anti hypertension drug was formulated as an Mouth dissolving tablet as there is a need to develop a formulation for this drug which overcomes problem such as difficulty in swallowing, inconvenience in administration while traveling and better compliance. Nebivolol HCl Mouth dissolving tablets were prepared by sublimation method and different concentration super disintegrants like Croscarmellose sodium, polyplasdone XL and Explotab were used in mouth dissolving tablets. A total of 9 formulations were prepared and evaluated for various pre and post compression parameters like angle of repose, bulk density, tapped density, carr's index, hausner's ratio, weight variation, hardness, friability, thickness, wetting time, water absorption ratio, drug content, *in vitro* disintegration time, *in vitro* drug release. The *in vitro* disintegration time of the optimised formulation (F4) of Nebivolol was found to be 7 sec. Release rate of drug was 97.54% within 10 minutes. FTIR studies showed good compatibility between drug and excipients.

Key words: Nebivolol HCl, Croscarmellose sodium, polyplasdone XL and Explotab, Mouth dissolving tablets.

1. INTRODUCTION

The oral route of administration is considered as the most widely accepted route because of its convenience of self administration, compactness and easy manufacturing. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients in compliance particularly in case of paediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or travelling, especially those who have no access to water.

For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Oral dispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people.¹

A Mouth disintegrating tablet (MDT) is a solid dosage form that contains medicinal substances and disintegrates rapidly (within seconds) without water when placed on the tongue. The drug is released, dissolved, or dispersed in the saliva, and then swallowed and absorbed across the GIT.²

US FDA defined MDT tablets as "A solid dosage form containing medicinal substances which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue".

Recently European Pharmacopoeia used the term 'Orodispersible tablet' as a tablet that is to be placed in the mouth where it disperses rapidly before swallowing.

Mouth disintegrating tablets are also called as mouth-dissolving tablets, fast disintegrating tablets, fast dissolving tablets, orodispersible tablets, rapimelts, porous tablets, quick dissolving tablet'.

The US Food and Drug Administration responded to this challenge with the 2008 publication of Guidance for Industry: Mouth Disintegrating Tablets (Rosie et al., 2009). Three main points stand out in the final guidance:

- ♦ MDTs should have an *in vitro* disintegration time of approximately 30sec or less.
- ♦ Generally, the MDT tablet weight should not exceed 500 mg, although the combined influence of tablet weight, size, and component solubility all factor into the acceptability of an MDT for both patients and regulators.

* VARIOUS TECHNOLOGIES USED IN FORMULATION OF MDT

The technologies that have been used by various researchers to prepare Mouth disintegrating dosage forms include: Patented and Non patented technologies.

Table 1.1: Patented and Non- patented technologies

Non -patented	Patented
Freeze drying	Zydus technology
Spray drying	Orosolv technology
Molding	Durosolv technology
Phase transition process	Wowtab technology
Melt granulation	Fashtab technology
Sublimation	Oraquick technology
Mass extrusion	Lyoc technology
Cotton candy process	Quick –Dis technology
Direct compression	Nanocrystal technology
Nanonization	Frosta technology
Effervescent method	Pharmaburst technology
	Flash Dose technology
	Ziplet/Advatab technology
	QuickSolv technology

PATENTED TECHNOLOGIES

ZYDIS TECHNOLOGY

- ◆ Scherer has patented the Zydis technology. Zydis, the best known of the fast dissolving/disintegrating tablet preparations, was the first marketed new technology tablet. The tablet dissolves in the mouth within seconds after placement on the tongue.
- ◆ A Zydis tablet is produced by lyophilizing or freeze-drying the drug in a matrix usually consisting of gelatin. The product is very lightweight and fragile, and must be dispensed in a special blister pack.
- ◆ Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet. The Zydis product is made to dissolve on the tongue in 2 to 3 seconds.
- ◆ In addition, it utilizes microencapsulation with specialized polymers or complexation with ion exchange resins to mask the bitter tasting drug. The combination of lyophilisation and taste masking creates a product that is both pleasing to the eye and also to the senses of taste and touch.

WOWTAB TECHNOLOGY

- ◆ The Wowtab fast-dissolving/disintegrating tablet formulation has been on the Japanese market for a number of years. Wowtab technology is patented by Yamanouchi Pharmaceutical Co. The WOW in Wowtab signifies the tablet is to be given "With out. Water". It has just recently been introduced into the U.S.
- ◆ This technology utilizes sugar and sugar-like (e.g., mannitol) excipients. This process uses a combination of low mouldability saccharides (rapid dissolution) and high mouldability saccharide(good binding property).
- ◆ The two different types of saccharides are combined to obtain a tablet formulation with adequate hardness and fast dissolution rate. Due to its significant hardness, the Wowtab formulation is a bit more stable to the environment than the Zydis or OraSolv.

FROSTA TECHNOLOGY

- ◆ Akina patents this technology. It utilizes the concept of formulating plastic granules and compressing them at low pressure to produce strong tablets with high porosity. Plastic granules composed of porous and plastic material, water penetration enhancer, and binder.

- ♦ The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 sec depending on size of tablet.

ORASOLV TECHNOLOGY

- ♦ OraSolv was Cima's first fast-dissolving/disintegrating dosage form. The OraSolv technology, unlike Zydis, disperses in the saliva with the aid of almost imperceptible effervescence.
- ♦ The OraSolv technology is best described as a fast-disintegrating tablet; the tablet matrix dissolves in less than one minute, leaving coated drug powder. The taste masking associated with the OraSolv formulation is two-fold. The unpleasant flavor of a drug is not merely counteracted by sweeteners or flavors; both coating the drug powder and effervescence are means of taste masking in OraSolv.
- ♦ This technology is frequently used to develop over-the-counter formulations. The major disadvantage of this formulation is its mechanical strength because the Orasolv tablets are only lightly compressed. An advantage that goes along with the low degree of compaction of OraSolv is that the particle coating used for taste masking is not compromised by fracture during processing.

DURASOLV TECHNOLOGY

- ♦ DuraSolv is Cima's second-generation fast-dissolving/disintegrating tablet formulation, produced in a fashion similar to OraSolv and has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting. It is so durable that it can be packaged in either traditional blister packaging or vials.
- ♦ The tablets are prepared by using conventional tableting equipment and have good rigidity (friability less than 2%). The product is thus produced in a faster and more cost-effective manner.
- ♦ One disadvantage of this technology is that it is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressures on compaction.
- ♦ Unlike OraSolv, the structural integrity of any taste masking may be compromised with high drug doses. The drug powder coating may become fractured during compaction, exposing the bitter-tasting drug to a patient's taste buds.
- ♦ Therefore, the DuraSolv technology is best suited for formulations including relatively small doses of active compound

FLASH DOSE TECHNOLOGY

- ♦ Fuisz Technologies has three oral drug delivery systems that are related to fast dissolution. The first two generations of quick-dissolving tablets, Soft Chew and EZ Chew, require some chewing. However, these paved the way for Fuisz's most recent development, Flash Dose.
- ♦ The Flash Dose technology utilizes a unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy. This crystalline sugar can then incorporate the active drug and be compressed into a tablet. This procedure has been patented by Fuisz and is known as Shear form.
- ♦ The final product has a very high surface area for dissolution. It disperses and dissolves quickly once placed onto the tongue. Interestingly, by changing the temperature and other conditions during production, the characteristics of the product can be altered greatly.

FLASHTAB TECHNOLOGY

- ♦ Prographarm laboratories has patented the Flashtab technology. This technology involves the preparation of rapidly disintegrating tablet which consists of an active ingredient in the form of microcrystals.
- ♦ Drug microgranules may be prepared by using the conventional techniques like coacervation, extrusion-spheronization, simple pan coating methods and microencapsulation.

- ♦ The microcrystals of micro-granules of the active ingredient are added to the granulated mixture of excipients prepared by wet or dry granulation, and compressed into tablets.
- ♦ All the processing utilized the conventional tableting technology, and the tablets produced are reported to have good mechanical strength and disintegration time less than one minute

ORAQUICK TECHNOLOGY

- ♦ The oraquick fast-dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. KV Pharmaceutical claims its microsphere technology, known as qMicro Mask, has superior mouth feel over taste masking alternatives. The taste masking process does not utilize solvents of any kind, and therefore leads to faster and more efficient production.
- ♦ Also, lower heat of production than alternative fast dissolving/ disintegrating technologies makes Ora Quick appropriate for heat-sensitive drugs.
- ♦ KV Pharmaceutical also claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable, meaning tablets can be compressed to achieve significant mechanical strength without disrupting taste masking .

QUICK –DIS TECHNOLOGY

- ♦ Lavipharm Laboratories Inc. (Lavipharm) has invented an ideal intraoral fast-dissolving drug delivery system, which satisfies the unmet needs of the market. The novel intraoral drug delivery system, trademarked Quick-Dis, is Lavipharm's proprietary patented technology and is a thin, flexible, and quick-dissolving film.
- ♦ The film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption.
- ♦ The Quick-Dis drug delivery system can be provided in various packaging configurations, ranging from unit-dose pouches to multiple-dose blister packages.

ZIPLETS/ADVATAB

- ♦ This technology is patented by passano con Barnago, Italy. It utilizes water-insoluble ingredient combined with one or more effective disintegrants to produce MDT with improved mechanical strength and optimal disintegration time at low compression force.
- ♦ This technology handles high drug loading and coated drug particles and does not require special packaging, so they can be packed in push through blisters or bottles.

LYOC

- ♦ Lyoc technology is patented by PHARMALYCO. Oil in water emulsion is prepared and placed directly into blister cavities followed by freeze-drying.
- ♦ Nonhomogeneity during freeze-drying is avoided by incorporating inert filler to increase the viscosity finally the sedimentation. High proportion of filler reduces porosity of tablets due to which disintegration is lowered.

PHARMABURST TECHNOLOGY

- ♦ SPI Pharma, New Castle, patents this technology. It utilizes the co-processed excipients to develop MDT, which dissolves within 30-40 s. this technology involves dry blending of drug, flavor, and lubricant followed by compression into tablets.
- ♦ Tablets obtained have sufficient strength so they can be packed in blister and bottles

NANOCRYSTAL TECHNOLOGY

- ♦ This is patented by Elan, King of Prussia. Nanocrystal technology includes lyophilization of colloidal dispersions of drug substance and water-soluble ingredients filled in to blister pockets.

- ◆ This method avoids manufacturing process such as granulation, blending, and tableting, which is more advantageous for highly potent and hazardous.

QUICK SOLV

- This technology is patented by Janssen Pharmaceuticals. It utilizes two solvents in formulation a matrix, which disintegrates instantly. Methodology includes dissolving matrix components in water using an excess of alcohol (solvent extraction).
- Thus the product formed has uniform porosity and adequate strength for handling.

NON PATENTED TECHNOLOGIES

Various conventional technologies used in the manufacture of MDT are classified into two types based on their procedures.

I, Technologies Employing Heating Process.

II. Technologies not Employing Heating Process.

FREEZE-DRYING OR LYOPHILISATION

Freeze drying (lyophilisation) is a process in which solvent is removed from a frozen drug solution or a suspension containing structure-forming excipients. The resulting tablets are usually very light and have highly porous structures that allow rapid dissolution or disintegration. When placed on the tongue, the freeze dried unit dissolves almost instantly to release the incorporated drug. The entire freeze drying process is done at non elevated temperatures to eliminate adverse thermal effects that may affect drug stability during processing.

- ◆ The tablets prepared by lyophilisation disintegrate rapidly in less than 5 sec due to quick penetration of saliva in pores when placed in the oral cavity. Lyophilisation is useful for heat sensitive drugs i.e. thermo-labile substances (Manoj et al., 2010).
- ◆ A typical procedure involved in the manufacturing of MDT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is dosed by weight and poured in the wells of the preformed blister packs.
- ◆ The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminium foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped.
- ◆ The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The major disadvantages of lyophilisation technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions (Guptha et al., 2010).

SPRAY DRYING

- ◆ Spray drying methods are widely used in pharmaceutical and biochemical processes. Spray drying provides a fast and economical way of removing solvents and producing highly porous, fine powders. Spray drying can be used to prepare rapidly disintegrating tablets.
- ◆ This technique is based on a particulate support matrix, which 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 active ingredients and compressed into tablet. (Kuldeep et al., 2010).
- ◆ Allen et al used a spray drying technique to prepare fast dissolving tablets. The tablets made from this technology are claimed to disintegrate within 20 seconds.

MOLDING

- ◆ Molded tablets disintegrate more rapidly and offer improved taste due to water soluble sugars present in dispersion matrix. Different molding techniques can be used to prepare Mouth disintegrating tablets.

COMPRESSION MOLDING (SOLVENT METHOD)

- ♦ The manufacturing process of molding tablets involves moistening the powder blend with a solvent (usually ethanol or water), and then the mixture is molded into tablets under pressures lower than those used in conventional tablet compression (Yourong et al., 2004).
- ♦ The solvent is then removed by air drying. Because molded tablets are usually compressed at a lower pressure than conventional compressed tablets, a higher porous structure is created to enhance the dissolution.

HEAT MOLDING

- ♦ A molten matrix in which drug is dissolved or dispersed can be directly molded into Mouth disintegrating tablets. The tablets prepared using heat molding process involves settling of molten mass that contains a dispersed or dissolved drug.
- ♦ The heat-molding process uses an agar solution as a binder and a blister packaging well as a mold to manufacture a tablet. The process involves preparing a suspension that contains a drug, agar, and sugar (e.g., mannitol or lactose), pouring the suspension into the blister packaging well, solidifying the agar solution at room temperature to form a jelly, and drying at -30°C under vacuum (Tejvir et al., 2011).

NO-VACUUM LYOPHILIZATION

- ♦ The process involves the evaporation of a solvent from a drug solution or suspension at standard pressure.
- ♦ Pebley et al., evaporated a frozen mixture containing a gum (e.g., acacia, carageenan, guar, tragacanth, or xanthan), a carbohydrate (e.g., dextrose, lactose, maltose, mannitol, or maltodextrin), and a solvent in a tablet shaped mould.
- ♦ Molded tablets typically do not possess great mechanical strength. Erosion and breakage of the molded tablet often occur during handling and opening of blister packs.
- ♦ In order to overcome this problem, binding agent such as sucrose, acacia, or polyvinylpyrrolidone must be added to the solvent system, but then the rate of tablet solubility usually decreases. MDTs, having both adequate mechanical strength and good disintegration, recently have been prepared by molding techniques using nonconventional equipment and/ or multistep processes. The nonconventional approach, however, does cost more.
- ♦ Compared with freeze drying, MDTs prepared by molding techniques can be produced more simply and efficiently at an industrial scale, although they cannot achieve disintegration times comparable with those of lyophilized forms.

PHASE TRANSITION PROCESS

- ♦ The combination of low and high melting point sugar alcohols, as well as a phase transition in the manufacturing process, is important for making Mouth disintegrating tablets without any special apparatus.
- ♦ Here, tablets produced by compressing the powder containing two sugar alcohols of high and low melting point and subsequently heating at temperature between their two melting points.
- ♦ MDT's were produced by compressing powder containing erythritol (melting point: 1220C) and xylitol (melting point 93 - 950C) and then heating at about 930C for 15min. After heating the median pore size of the tablets was increased and tablet hardness was also increased.
- ♦ The increase of tablet hardness with heating and storage did not depend on the crystal state of the lower melting point of the sugar alcohol (Manoj et al.,

MELT GRANULATION

- ♦ Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a meltable binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed.

- ♦ Because there is no drying step, the process is less time consuming and uses less energy than wet granulation. It is a useful technique to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin MDT was prepared by incorporating a hydrophilic waxy binder (super polystate) PEG- 6-Sterate. Superpolystate is a waxy material with a melting point of 33-37°C and hydrophilic lipophilic balance of 14
- ♦ It is not only acts as a binder and increases the physical resistance of tablets, but also helps the disintegration of tablets as it melts in the mouth and solubilizes rapidly leaving no residue in oral cavity (Abdelbary et al., 2009).
- ♦ Carbamazepine fast release tablets were prepared by melt granulation technique using PEG – 4000 as a melting binder and lactose monohydrate as hydrophilic filler.

SUBLIMATION

- ♦ Sublimation has been used to produce MDTs with high porosity. A porous matrix is formed by compressing the volatile ingredients along with other excipients into tablets, which are finally subjected to a process of sublimation.
- ♦ Removal of volatile material by sublimation creates pores in tablet structure, due to which tablet dissolves when comes in contact with saliva. Inert solid ingredients with high volatility (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylene tetramine, naphthalene, phthalic anhydride, urea and urethane) have been used for this purpose (Rangasamy et al., 2009).
- ♦ Solvents such as cyclohexane and benzene were also suggested for generating the porosity in the matrix. Mouth dissolving tablets with highly porous structure and good mechanical strength have been developed by this method. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva.
- ♦ MDT were developed by utilizing camphor; a subliming material that is removed from compressed tablets prepared using a mixture of mannitol and camphor. Camphor was sublimated in vacuum at 80°C for 30 min after preparation of tablets.
- ♦ Fast-dissolving tablet were developed by using water as the pore-forming material. A mixture containing an active ingredient and a carbohydrate (preferably sucrose, glucose, xylitol, or erythritol) was moistened with water (1-3% by weight) and compressed into tablets. The water was then removed, yielding highly porous tablets that exhibited excellent mechanical strength and a high dissolution rate.

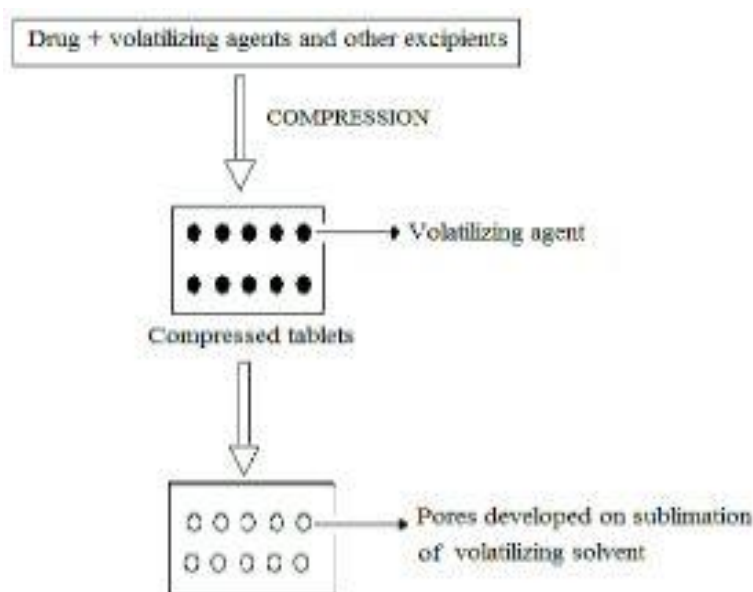


Fig.: Steps Involved in Sublimation (Kuldeep et al., 2010)

MASS-EXTRUSION

- ◆ This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablet.
- ◆ The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking.

COTTON CANDY PROCESS

- ◆ The cotton candy process is also known as the “candy floss” process and forms the basis of the technologies such as Flash Dose (Fuisz Technology). There are various pre blend mixtures used in the manufacture of ‘floss’, few of which are summarized in table.

Table: Various preblend compositions used in floss process

Floss pre blend compositions	Drugs
Sucrose (78.25%), Sorbitol (11%), Xylitol (10%) and Tween 80 (0.75%)	Ibuprofen, Cimetidine, Vitamine C, Calcium carbonate/Vitamine D or Acetaminophen
Sucrose (84.5%), Mannitol (5%), Sorbitol (5%), Xylitol (5%) and Polysorbate 80 (0.5%)	Ibuprofen, Cimetidine, Vitamine C, Calcium carbonate/Vitamine D or Acetaminophen
Sucrose (84.75%), Sorbitol (12%), α – Lactose (3%) and Tween 80 (0.25%)	Ibuprofen, Aspirin, Acetaminophen

- This process is so named as it utilizes a unique spinning mechanism to produce floss like crystalline structure which mimics cotton candy. This process involves formation of matrix of polysaccharide or saccharide by simultaneous action of flash melting and spinning.
- The matrix formed is partially re crystallized to have improved flow property and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed in to an MDT.
- This process can accommodate high dose of drug and offers improved mechanical strength, however high process temperature limits the use of this process to thermo stable compounds only (Bhatu et al., 2011).
- The FLASHDOSE is a MDDDS manufactured using Shearform™ technology in association with Ceform TI technology to eliminate the bitter taste of the medicament.
- The Shearform technology is employed in the preparation of a matrix known as ‘floss’, made from a combination of excipients, either alone or with drugs.
- The floss is a fibrous material similar to cotton-candy fibers, commonly made of saccharides such as sucrose, dextrose, lactose and fructose at temperatures ranging between 180–266 °F. However, other polysaccharides such as polymaltodextrins and polydextrose can be transformed into fibers at 30–40% lower temperature than sucrose.
- This modification permits the safe incorporation of thermo labile drugs into the formulation. The tablets manufactured by this process are highly porous in nature and offer very pleasant mouth feel due to fast solubilization of sugars in presence of saliva.

DIRECT COMPRESSION

- Direct compression is the easiest way to manufacture tablets and therefore, MDTs. The great advantage of direct compression is low manufacturing cost.
- It uses conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression.
- Moreover high doses can be accommodated and final weight of tablet can easily exceed that of other production methods (Dobetti et al., 2001).
- The direct compression tablet's disintegration and solubilisation are based on the single or combined action of disintegrants, water-soluble excipients, and effervescent agents.
- The disintegration time is, in general, satisfactory, although the disintegrating efficacy is strongly affected by tablet size and hardness. Large, hard tablets can have a disintegration time greater than that usually required for MDTs.

- As a consequence, products with optimal disintegration properties often have a medium-small size (weight) and/or a low physical resistance (high friability and low hardness) are formulated but breakage of tablet edges during handling, the presence of deleterious powder in the blistering phase, and tablet rupture during the opening of the blister alveolus, all result from insufficient physical resistance.
- In many cases the disintegrants have a major role in the disintegration and dissolution process of MDTs made by direct compression.
- The choice of a suitable type and an optimal amount of disintegrants is paramount for ensuring a high disintegration rate. The addition of other formulation components such as water soluble excipients or effervescent agents can further enhance dissolution or disintegration properties.
- The understanding of disintegrant properties and their effect on formulation has significantly advanced during the last few years, particularly regarding so called super disintegrants.
- This technique can now be applied to preparation of MDT because of the availability of improved excipients especially super disintegrants and sugar based excipients.

ADDITION OF SUPERDISINTEGRANTS

- In many Mouth disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution.
- The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

SUGAR BASED EXCIPIENTS

- This is another approach to manufacture MDT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltitol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouthfeel.
- Mizumoto et al have classified sugar-based excipients into two types on the basis of molding and dissolution rate. Type 1 saccharides (lactose and mannitol) exhibit low mouldability but high dissolution rate.
- Type 2 saccharides (maltose and maltitol) exhibit high mouldability and low dissolution rate (Debjit et al., 2009).

NANONIZATION

- A recently developed Nanomelt technology involves reduction in the particle size of drug to nanosize by milling the drug using a proprietary wet-milling technique.
- The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into MDTs. This technique is especially advantageous for poorly water soluble drugs (Guptha et al., 2010).
- Other advantages of this technology include fast disintegration/dissolution of nanoparticles leading to increased absorption and hence higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).

EFFERVESCENT METHOD

- Orodispersible tablets are also prepared by effervescent method by mixing sodium bicarbonate and tartaric acid of concentration 12% (w/w) along with super disintegrants like pregelatinized starch, sodium starch glycolate, croscopovidone, and croscarmellose. First, sodium bicarbonate and tartaric acid were preheated at a temperature of 80°C to remove absorbed/residual moisture and thoroughly mixed in the motor, finally the blends are compressed in the punch.

- The major advantages of this method are it is well established, easy to implement and mask the bitter taste of the drug. The effervescent system is generally composed of a dry acid and dry base which when react facilitate a mild effervescent action when the tablet contact with saliva.
- The effervescent reaction accelerates the disintegration of tablet through the release of carbon dioxide, water and salt. Due to the evolution of Carbon dioxide, the bitter taste of the drug is also masked and a pleasant mouth feel is felt. The major drawbacks of these methods includes chemical stability for which controlled humidity conditions required and storage conditions like temperature and hygroscopicity.

METHODOLOGY

1. CONSTRUCTION OF CALIBRATION CURVE OF NEBIVOLOL HCl pH 6.8 PHOSPHATE BUFFER

- Accurately weighed 10 mg of drug was transferred to 10 ml volumetric flask and dissolved in 10ml of methanol, this was considered as stock solution (I).
- To 1 ml of stock solution (I) 9 ml of pH 6.8 phosphate buffer was added and this was considered as stock solution (II).
- From stock solution (II) 0.2ml,0.4ml,0.6ml,0.8ml,1ml were taken and was made up the volume to 10ml with pH 6.8 phosphate buffer to get respective concentrations of 2,4,6,8 and 10 µg/ ml.
- Prepared samples were analyzed by using ultra violet double beam spectrophotometer at λ_{max} 274nm.
- The calibration curve was plotted by taking concentration on x-axis and absorbance on y-axis.

2. PREPARATION OF NEBIVOLOL HCl MOUTH DISSOLVING TABLETS

Preparation of NEBIVOLOL HCl Mouth dissolving tablets by direct compression method

- Drug and different concentrations of super disintegrates and sweetening agent were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass mortar for 15 minutes.
- The obtained blend was lubricated with magnesium stearate and glidant (Talc) was added and mixing was continued for further 5 minutes.
- The resultant mixture was directly compressed into tablets by using 6mm punch of rotary tablet compression machine. Compression force was kept constant for all formulations.

Table: Composition of Nebivolol HCL Mouth dissolving tablet

Materials (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nebivolol HCl	5	5	5	5	5	5	5	5	5
Croscarmellose sodium	5	10	15	-	--	-	-	-	-
Explotab	-	-	-	5	10	15	-	-	-
Polyplasdone XL	-	-	-	-	-	-	5	10	15
Talc	2	2	2	2	2	2	2	2	2
Mg stearate	2	2	2	2	2	2	2	2	2
Mannitol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight	100	100	100	100	100	100	100	100	100

3. EVALUATION OF PRE-COMPRESSION PARAMETERS OF POWDER BLEND

ANGLE OF REPOSE

- Angle of repose was determined using funnel method .The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) is obtained. Radius of the heap (r) was measured and angle of repose (θ) was calculated using the following formula.

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

Table: Angle of repose as an indication of powder flow properties

Sr. No	Angle of Repose (°)	Type of Flow
1	< 20	Excellent
2	20 – 30	Good
3	30 – 34	Passable
4	> 34	Very Poor

BULK DENSITY

- Apparent bulk density (ρ_b) was determined by pouring the powder blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) were determined.

$$\rho_b = M / V_b$$

TAPPED DENSITY

- The measuring cylinder containing a known mass of blend (M) was tapped for a fixed time (100 tapping). The minimum volume (V_t) occupied in the cylinder and weight of the blend was measured. The tapped density (ρ_t) was calculated using the following formula.

$$\rho_t = M / V_t$$

COMPRESSIBILITY INDEX OR CARR'S INDEX:

- The simplest way for measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index.

$$\text{Carr's Index} = \rho_b - \rho_t / \rho_b * 100$$

Where ρ_t = tapped density

ρ_b = bulk density

Table: Relationship between compressibility and flow ability

% Compressibility	Flow ability
5 – 12	Excellent
12 – 16	Good
18 – 21	Fair Passable
23 – 35	Poor
33 – 38	Very Poor
< 40	Very Very Poor

HAUSNER'S RATIO (H)

- Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula:

$$\text{Hausner's ratio (H)} = \rho_t / \rho_b$$

Where ρ_t = tapped density

ρ_b = bulk density

4. EVALUATION OF POST COMPRESSION PARAMETERS OF NEBIVOLOL HCL MDTs:

- Different quality control tests were performed for all the MDT formulations to check whether these have met the specifications given in USP along with other *In-vitro* tests like wetting time and water absorption ratio.

Various tests performed are:

- Weight variation test
- Thickness measurement
- Hardness

- Friability
- Drug Content uniformity
- Wetting time and Water absorption ratio
- In vitro dispersion Time
- In vitro disintegration Time
- In vitro dissolution studies
- Moisture uptake studies

WEIGHT VARIATION TEST

- **Method:** 20 tablets were randomly selected from each formulation and their individual weights and average weight of all 20 tablets was calculated by weighing on an electronic balance (Shimadzu, AUX 220, Shimadzu Corp, Japan). The Mean \pm S.D. were noted.

Table: Weight Variation Limits

IP/BP	Limit	USP
80 mg or less	10%	130mg or less
More than 80mg or Less than 250mg	7.5%	130mg to 324mg
250mg or more	5%	More than 324mg

THICKNESS

- **Method:** Randomly 10 tablets were taken from each formulation and their thickness was measured using a Micrometer. Average thickness and standard deviation values were calculated. The tablet thickness should be controlled within a $\pm 5\%$ variation of standard value.

HARDNESS

- **Method:** The tablet hardness of different formulations was measured using the Monsanto hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet, and a zero was taken.
- The upper plunger was then forced against the spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is recorded, and the zero force reading is deducted from it. Generally, a minimum hardness of 2.5 kg / cm² is considered acceptable for uncoated tablets.
- The hardness for MDTs should be preferably 2.5 to 3 kg / cm².

FRIABILITY

- **Method:** This test was performed using a laboratory friability tester known as Roche friabilator. 20 tablets were weighed and placed in a plastic chambered friabilator attached to a motor, which revolves at a speed of 25 rpm, dropping the tablets from a distance of 6 inches with each revolution. The tablets were subjected to 100 revolutions for 4 minutes. After the process, these tablets were de-dusted and reweighed. Percentage loss of tablet weight was calculated. Friability values below 1% are generally acceptable.

$$\% \text{ Friability} = \frac{W_1 - W_2}{W_1} \times 100$$

Where W_1 = Initial weight of 10 tablets.

W_2 = Final weight of 10 tablets.

DRUG CONTENT

- **Method:** 3 tablets were randomly selected, weighed and finely powdered and quantity of powder equivalent to one tablet was added to 100 ml of 6.8pH phosphate buffer in a conical flask. A conical flask was then placed on a rotary shaker.
- An aliquot of solution was centrifuged and supernatant was filtered through a 0.22 μ filter. Absorbance of the resulted supernatant solution was measured using U.V Visible double beam spectrophotometer at a wavelength of 274 nm against 6.8pH phosphate buffer as blank. Concentrations and amount of drug present in one tablet were calculated with the help of calibration curves.

WETTING TIME

- **Method:** A piece of tissue paper folded twice was placed in a small petridish containing 6ml of water. A water-soluble dye phenolphthalein was added to the petridish. The dye solution was used to identify the complete wetting of the tablet surface (Abdelbary et al, 2009). A tablet was carefully placed on the surface of tissue paper in the petridish at room temperature.
- The time required for water to reach the upper surface of the tablets and completely wet them was noted as the wetting time. To check for reproducibility, the measurements were carried out in triplicates (n=3). The wetting time was recorded using a stopwatch.

WATER ABSORPTION RATIO (R)

- **Method:** The weight of the tablet before keeping in the petridish was noted (W_b) using digital balance. The wetted tablet from the petridish was taken and reweighed (W_a) using the same. The Water absorption ratio, R, was determined according to the following equation:

$$R = (W_a - W_b) / W_b * 100$$

W_a = Weight of the tablet after absorption
 W_b = Weight of the tablet before absorption

IN VITRO DISPERSION TIME

- **Method:** *In vitro* dispersion time was determined by placing one tablet in a beaker containing 10 ml of pH 6.8 phosphate buffer at $37 \pm 0.5^\circ\text{C}$ and the time required for complete dispersion was determined.
- To check for reproducibility, the measurements were carried out in triplicates (n=3). The dispersion time was recorded using a stopwatch.

IN VITRO DISINTEGRATION TIME

- **Method:** A piece of tissue paper folded twice was placed in a small petridish containing 6ml of pH 6.8 phosphate buffer. A tablet was carefully placed on the surface of tissue paper in the petridish at room temperature.
- The time required for water to reach the upper surface of the tablets and completely wet them and break down into small particles was noted as the *in vitro* disintegration time. To check for reproducibility, the measurements were carried out in triplicates (n=3). The disintegration time was recorded using a stopwatch.

IN VITRO DISSOLUTION STUDIES

- **Method:** Dissolution test was carried out by using USP type II apparatus. The paddle was rotated at 50 rpm. 6.8 Phosphate buffer was used as dissolution medium (500ml) and was maintained at $37 \pm 1^\circ\text{C}$. Samples of 5ml were withdrawn at predetermined intervals (5, 10, 15, 20 and 30), filtered and replaced with 5ml of fresh dissolution medium.
- The collected samples were suitably diluted with dissolution fluid, where ever necessary and were analyzed for the drug at 274 nm by using ultra violet double beam spectrophotometer. Each dissolution study was performed for three times and mean values were taken.

5. CHARACTERISATION

Fourier Transform Infrared Spectroscopy (FTIR)

- FTIR studies were performed on drug, optimised formulation using Bruker FTIR. The samples were analyzed between wave numbers 4000 and 400 cm^{-1} .

RESULTS AND DISCUSSION

DETERMINATION OF λ_{max} AND PREPARATION OF CALIBRATION CURVE OF NEBIVOLOL HCl

The regression coefficient was found to be 0.999 which indicates a linearity with an equation of $Y=0.0376x+0.003$. Hence Beer - Lambert's law was obeyed.

Table: Calibration curve data of Nebivolol HCl in 0.1N HCl at λ_{max} of 274nm

Concentration ($\mu\text{g/mL}$)	Absorbance
0	0
2	0.179
4	0.381
6	0.555
8	0.727
10	0.895

EVALUATION OF PRE - COMPRESSION PARAMETERS OF POWDER BLEND

Table: Evaluation of pre-compression parameters of powder blend

Formulation	Bulk Density* (g/mL)	Tapped density* (g/mL)	Carr's index* (%)	Angle of Repose* (θ)	Hausner's ratio*
F 1	0.50 \pm 0.04	0.59 \pm 0.05	15.25 \pm 0.04	27 \pm 0.05	1.18 \pm 0.08
F2	0.47 \pm 0.05	0.56 \pm 0.06	16.07 \pm 0.06	25 \pm 0.02	1.20 \pm 0.08
F3	0.52 \pm 0.05	0.60 \pm 0.06	13.3 \pm 0.04	29 \pm 0.02	1.21 \pm 0.09
F4	0.46 \pm 0.08	0.55 \pm 0.03	16.36 \pm 0.05	25 \pm 0.06	1.16 \pm 0.07
F5	0.43 \pm 0.06	0.53 \pm 0.02	18.86 \pm 0.05	26 \pm 0.08	1.22 \pm 0.07
F6	0.50 \pm 0.07	0.60 \pm 0.07	16.66 \pm 0.04	26 \pm 0.07	1.20 \pm 0.08
F7	0.48 \pm 0.06	0.56 \pm 0.07	14.28 \pm 0.06	28 \pm 0.06	1.20 \pm 0.06
F8	0.52 \pm 0.06	0.60 \pm 0.02	13.33 \pm 0.03	28 \pm 0.06	1.19 \pm 0.06
F9	0.47 \pm 0.07	0.56 \pm 0.02	16.07 \pm 0.06	27 \pm 0.08	1.20 \pm 0.08

* Results are the mean of 3 observations \pm SD

- For each formulation blend of drug and excipients were prepared and evaluated for various precompression parameters
- The bulk density of all formulations was found in the range of (0.43 \pm 0.05 - 0.54 \pm 0.08) and tapped density was in range of (0.50 \pm 0.06 - 0.65 \pm 0.07).
- The Carr's index and Hausner's ratio was calculated from tapped density and bulk density.
- The powder blend of all six formulations with Hausner's ratio < 1.25 and Carr's index < 18 indicates good flow ability of all powder blends
- The flow properties for all the powder blends were good as evidenced by the angle of repose values obtained, which ranged between (25 \circ – 30 \circ) which is less than 30 \circ as greater than 30 \circ has poor flow ability which has been observed in case of pure drug.

EVALUATIONS OF POST COMPRESSION PARAMETERS OF NEBIVOLOL HCl MDTs

Table: Evaluation of post compression parameters of Nebivolol HCl Mouth dissolving tablet (1)

Formulation	Average Weight *	Thickness (mm)**	Hardness** Kg/cm^2	% Friability*	Drug content**
F1	98.4 \pm 1.35	3.32 \pm 0.05	2.5 \pm 0.05	0.62 \pm 0.08	98.85 \pm 0.54
F2	105.2 \pm 1.12	3.28 \pm 0.04	2.4 \pm 0.03	0.58 \pm 0.06	99.7 \pm 0.38
F3	99.8 \pm 1.05	3.45 \pm 0.06	2.5 \pm 0.05	0.65 \pm 0.06	99.54 \pm 0.67
F4	100.3 \pm 1.24	3.38 \pm 0.06	2.5 \pm 0.06	0.62 \pm 0.05	99.86 \pm 0.56
F5	99.6 \pm 1.31	3.51 \pm 0.08	2.4 \pm 0.08	0.66 \pm 0.04	100.45 \pm 0.36
F6	102.2 \pm 1.02	3.38 \pm 0.07	2.3 \pm 0.09	0.58 \pm 0.04	98.64 \pm 0.68
F7	103.7 \pm 1.46	3.46 \pm 0.06	2.5 \pm 0.07	0.66 \pm 0.05	99.76 \pm 0.53
F8	97.8 \pm 1.18	3.54 \pm 0.05	2.3 \pm 0.05	0.60 \pm 0.03	101.56 \pm 0.67
F9	98.15 \pm 1.14	3.29 \pm 0.08	2.3 \pm 0.8	0.59 \pm 0.04	98.14 \pm 0.54

* Results are the mean of 10 observations \pm SD, **Results are the mean of 5 observations \pm SD

**Results are the mean of 3 observations \pm SD

- **Weight variation and thickness:** All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown in table 8.3. The average tablet weight of all the formulations was found to be between (**97.8 ± 1.18 to 105.2±1.12**). The maximum allowed percentage weight variation for tablets weighing 80-250 mg by I.P is 7.5% and no formulations are exceeding this limit. Thus all the formulations were found to comply with the standards given in I.P.
- **Hardness and friability:** All the MDT formulations were evaluated for their hardness, using Monsanto hardness tester and the results are shown in table 8.3. The average hardness for all the formulations was found to be between (2.3±0.05 to 2.5 ±0.07) Kg/cm² which was found to be acceptable (Avinash et al., 2010).
- **Friability** was determined to evaluate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the MDT formulations were evaluated for their percentage friability using Roche friabilator and the results are shown in table 8.3. The average percentage friability for all the formulations was between 0.58 ± 0.05 and 0.66± 0.06, which was found to be within the limit.
- **Drug content:** All the formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown in table 8.3. The assay values for all the formulations were found to be in the range of (98.64 ±0.068 to 101.56±0.67). According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the MDT formulations comply with the standards given in IP.

Table: Evaluation of post compression parameters of Nebivolol HCl Mouth dissolving tablets (2)

Formulation	Disintegration time*(seconds)	Wetting time* (seconds)	In vitro dispersion time*(sec)	%Water absorption ratio*
F1	15	13	16	88
F2	13	10	13	91
F3	9	8	8	97
F4	7	5	5	98
F5	16	13	14	90
F6	13	11	12	93
F7	11	9	11	98
F8	8	6	9	98
F9	14	12	16	92

* Results are the mean of 3

- **In vitro disintegration time:** *In vitro* disintegration studies showed from 7 to 16 secs. These results indicate that increasing the concentration of super disintegrates in the tablets results in the formation of more cohesive tablets that are less likely to break up or dissolve easily in water.
- **Wetting time:** Wetting time to the time required to wet completely when kept motionless on the tissue paper in a petridish.
- All the MDT formulations were evaluated for their wetting time as per the procedure described in the methodology section, and the results are shown in table 8.4.
- The average wetting time for all the formulations was in the range of (**5 to 13**) seconds.
- It was also observed that formula F4 which had the least wetting time also had the minimum disintegration time showing a strong correlation between disintegration time and wetting time.

In vitro dispersion time: Nebivolol HCl MDTs F4 containing Explotab dispersed time is 5secs. The dispersion time of formulations (F4) containing Explotab was lower than those containing croscarmellose and polyplasdone XL. The *in vitro* dispersion time for all formulation was found to be in a range of **5 to 16** seconds

Water Absorption ratio: All the formulations were evaluated for water absorption ratio according to the procedure described in methodology section and the results are shown in table 8.4.

- The maximum water absorption ratio was shown by formulation F4, F7, F8 showed **98%**.
- Water absorption ratio is proportional to dissolution rate profile as higher the water absorption ratio faster the dissolution.

Table: *In Vitro* dissolution study of Nebivolol HCl MDT tablets

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	25.4	30.8	45.72	75.33	33.45	25.34	45.75	67.15	42.74
10	39.6	36.72	66.16	97.54	51.25	35.42	65.24	82.26	72.41
15	48.6	56.16	101.16		64.12	46.15	80.14	99.34	96.32
20	64.3	87.4			75.12	55.64	99.15		96.32
30	76.4	99.5			83.14	67.12			
45	86.4				100.26	75.48			
60	99.56					87.43			

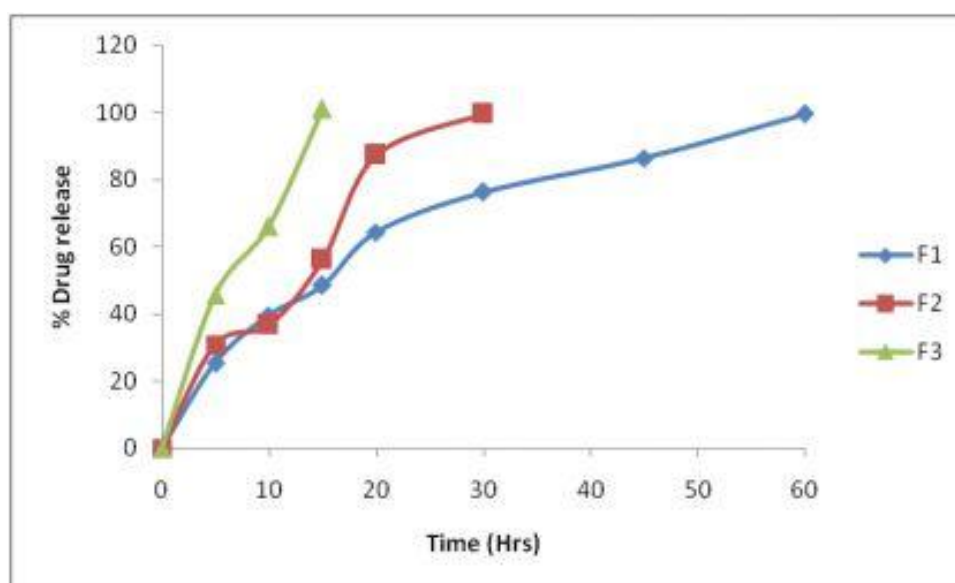


Fig.: In vitro drug release of Nebivolol HCl MDT tablets containing Croscarmellose sodium(F1-F3)

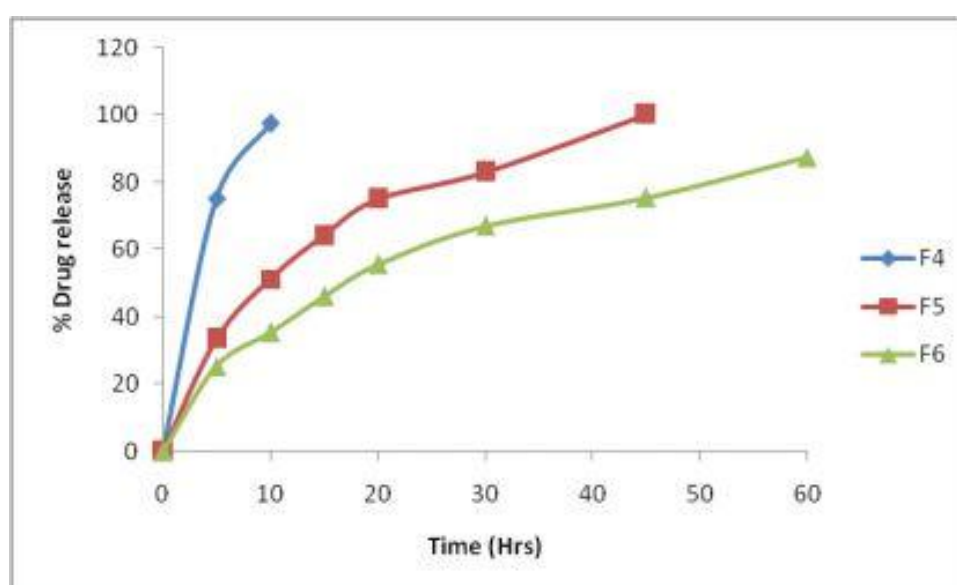


Fig.: In vitro drug release of Nebivolol HCl MDT tablets containing Explotab(F4-F6)

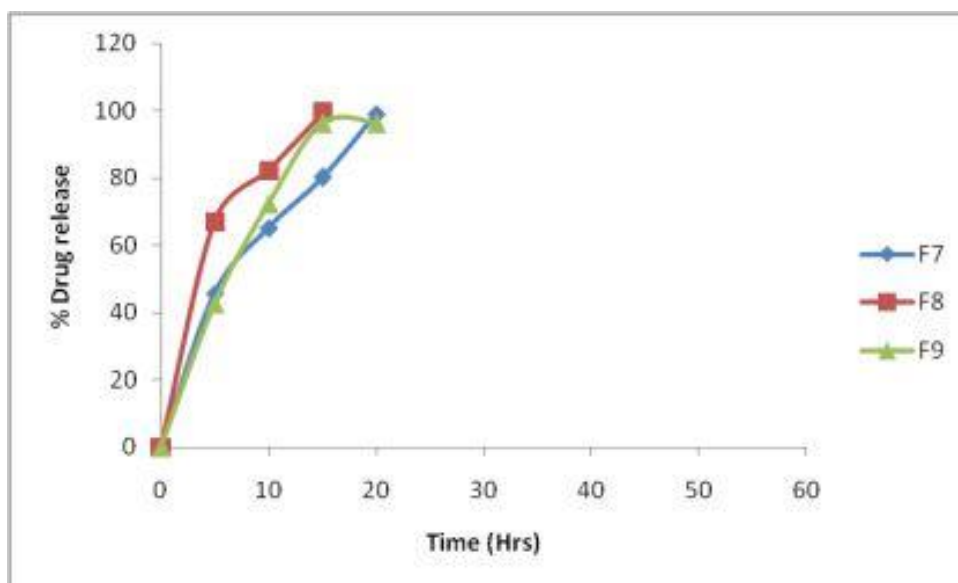


Fig.: In vitro drug release of Nebivolol HCl MDT tablets containing Polypladsone XL (F7-F9)

From the above dissolution data, all the formulations prepared with croscarmellose sodium, Explotab and Polypladsone XL were shown good drug release within 60 min.

Formulations containing croscarmellose sodium were shown drug release as increase the concentration shows good drug release. Whereas Explotab containing formulations increase the concentration retards the drug release.

Formulations containing polypladsone XL similar drug release in all concentration. Among formulations (F1-F9), formulation F4 was considered as optimised formulation due to maximum drug release within 10 min. i.e. 97.54%

FTIR RESULTS:

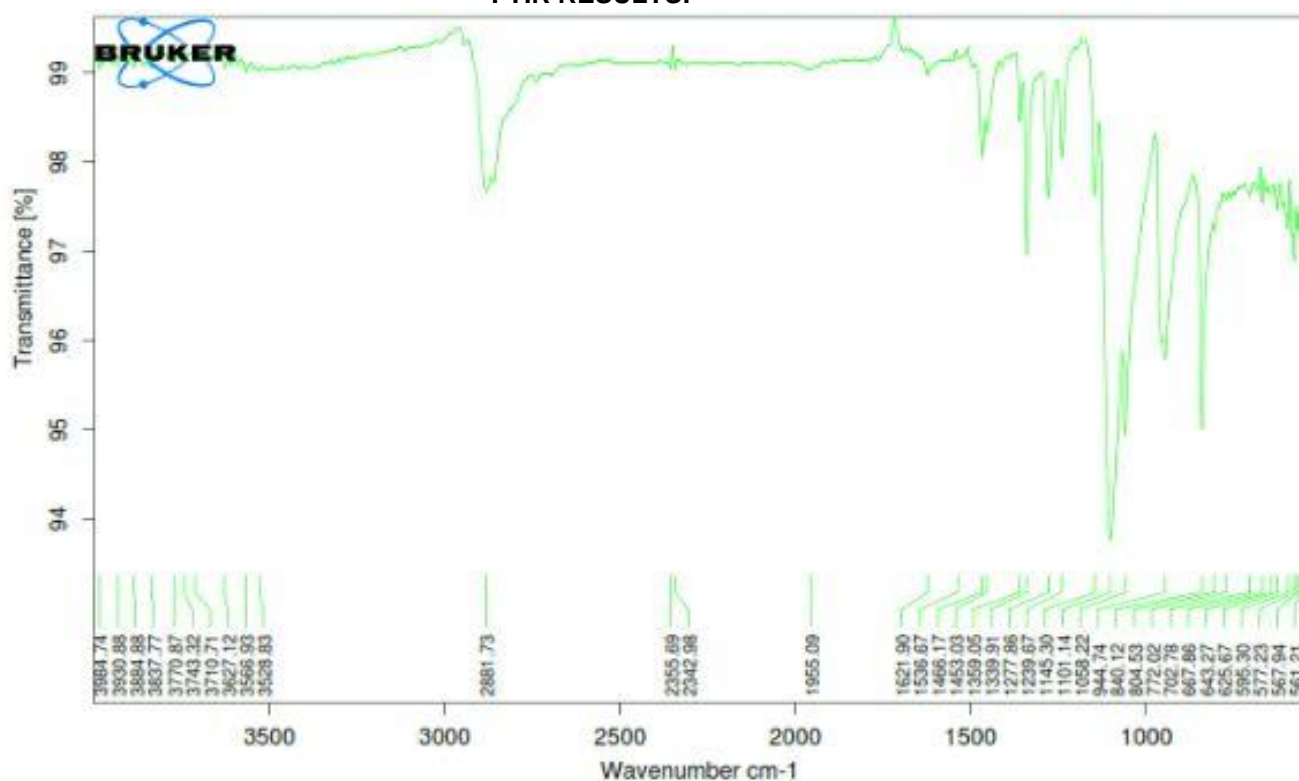


Fig.: FT-IR of pure drug

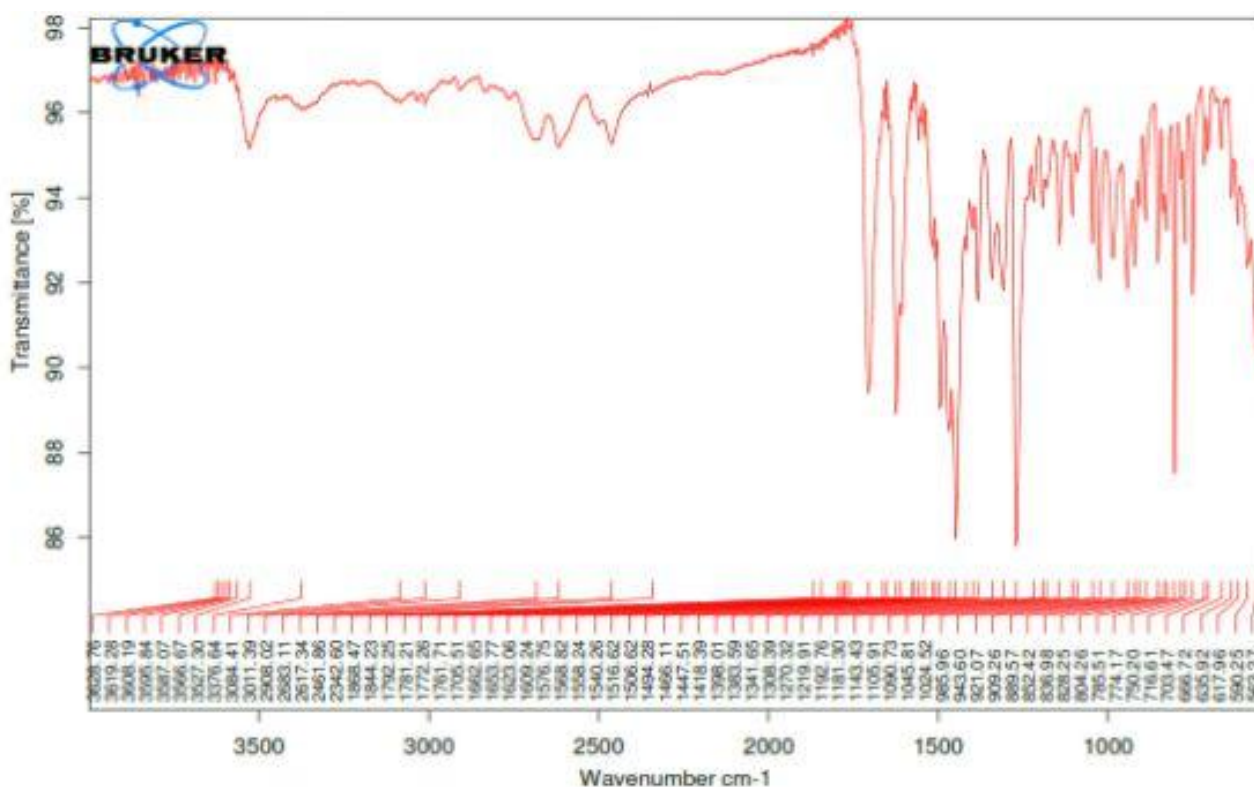


Fig.: FT-IR of optimised formula

From the FTIR data it was evident that the drug and excipients doses not have any interactions. Hence they were compatible.

CONCLUSION

Novel drug delivery system and formulation research are oriented towards increasing safety and efficacy of existing drug molecule through novel concepts of drug delivery. As precision of dosing and patient's compliance become important prerequisite for quick relief from Hyper tension, an anti hypertension drug was formulated as an Mouth dissolving tablet as there is a need to develop a formulation for this drug which overcomes problem such as difficulty in swallowing, inconvenience in administration while traveling and better compliance. Nebivolol HCL Mouth dissolving tablets were prepared by sublimation method and different concentration super disintegrants like croscarmellose sodium, polyplasdone XL and Explotab were used in mouth dissolving tablets. A total of 9 formulations were prepared and evaluated for various pre and post compression parameters like angle of repose, bulk density, tapped density, carr's index, hausner's ratio, weight variation, hardness, friability, thickness, wetting time, water absorption ratio, drug content, *in vitro* disintegration time, *in vitro* drug release. The *in vitro* disintegration time of the optimised formulation (F4) of Nebivolol was found to be 7 sec. Release rate of drug was 97.54% within 10 minutes. FTIR studies showed good compatibility between drug and excipients.

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