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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF AMIODARONE HCL BY USING NATURAL SUPERDISINTEGRANTS

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ABSTRACT

Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. For the treatment of human diseases, nasal and pulmonary routes of drug delivery are gaining increasing importance. These routes provide promising alternatives to parenteral drug delivery. Development of new drug molecule is expensive and time consuming. Improving safety efficacy ratio of "old" drugs has been attempted using different methods such as individualizing drug therapy, dose titration, and therapeutic drug monitoring. The conventional dosage forms (tablet and capsule) have wide acceptance up to 50-60% of total dosage forms. Tablet is still most popular conventional dosage forms existing today because of ease of self administration, compact in nature, easy to manufacture and it can be deliver in accurate dose. Amiodarone is an antiarrhythmic medication used to treat and prevent a number of types of irregular heartbeats. Amiodarone HCl is a white to cream-colored crystalline powder. It contains 37.3% iodine by weight. Tablet disintegration has been considered as the rate limiting step in faster drug release. Natural gums and mucilages have been widely explored as pharmaceutical excipients. These are widely used in the pharmaceutical industry as thickener, emulsifier, stabilizer, gelling agent, granulating agent, suspending agent, binder, film former, disintegrant and as sustained release matrix.

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INTRODUCTION

Drug delivery system is an efficient tool for enhancing market, extending product life cycles and creating opportunities. Drug delivery system (DDS) makes a significant contribution to global pharmaceutical sales through market segmentation, and is moving rapidly (Ahmed *et al*., 1993). Despite of tremendous innovations in drug delivery, the oral route remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self medication, non invasive method and ease of administration leading to high level of patient compliance (Amin *et al*., 2005). The most popular dosage forms are being conventional tablets and hard gelatin capsules. One study showed that approximately 26% of 1576 patients do not take their prescribed medication as they encountered problems when swallowing conventional tablets. Often, the main complaints are the size, surface and taste of the tablets. An estimated 35% of the general population, and an additional 30–40% of elderly institutionalized patients and 18–22% of all persons in long-term care facilities, suffer from dysphagia. This disorder is associated with many medical conditions, including stroke, Parkinson's, AIDS, thyroidectomy, head and neck radiation therapy, and other neurological disorders, including cerebral palsy. The conventional dosage forms (tablet and capsule) have wide acceptance up to 50-60% of total dosage forms. Tablet is still most popular conventional dosage forms existing today because of ease of self administration, compact in nature, easy to manufacture and it can be deliver in accurate dose. One important drawback of solid dosage forms is the difficulty in swallowing (dysphagia) or chewing in some patients particularly pediatric and geriatric patients. The problem of swallowing is common phenomenon in geriatric patient due to fear of choking, hand tremors, dysphasia and in young individuals due to underdeveloped muscular and nervous systems and in schizophrenic patients which leads to poor patient compliance. Difficulties in swallowing of tablet and capsule are also occur when water is not available, in diarrhea, coughing during the common cold, allergic condition and

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bronchial infection (Ananda and Kandarapub, 2007). Recent advances in the novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance i.e., one which will rapidly disintegrate or dissolve in the mouth without the need of water, mouth dissolving tablets (MDT) (Biradar *et al*., 2006; Biraju patel *et al*., 2009). The Center for Drug Evaluation and Research (CDER), US FDA defined Mouth dissolving/ disintegrating tablets (MDDTs) are "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". Recently European Pharmacopoeia also adopted the term Oro Dispersible Tablet defined as uncovered tablet for buccal cavity, where it disperses before ingestion. Mouth disintegrating tablets (MDT) are also known as fast dissolving, rapid-dissolve, quick disintegrating, orally disintegrating, rapimelt, fast melts, orodispersible, melt-in-mouth, quick dissolving, porous tablets, EFVDAS or Effervescent Drug Absorption System (Bhalerao *et al*., 2009). Taste-masking is of critical importance in the formulation of an acceptable FDDT. Traditional tablet formulations generally do not address the issue of taste masking, because it is assumed that the dosage form will not dissolve until passing the oral cavity. Elimination of the bitterness of the tablet can be acheived by adding flavors and sweetening agent or by sugar coating on the tablets. To increase the tablet disintegration, superdisintegrants are added in it, which are very helpful to increase the bioavailability of tablet and to increase the disintegration property of tablet in saliva. The patients can feel the normal disintegration time of MDT's from 5-30 sec. MDT's are mainly prepared by various methods like direct compression, wet granulation, solid dispersion and tablet molding etc. Direct compression method is the most widely used and easiest or cost effective method for MDT's as compared to other methods.

Requirements of mouth dissolving tablets

- Have a pleasing mouth feel
- Have an acceptable taste masking property
- Should be harder and friable
- Leave minimal or no residue in the mouth after oral administration
- Exhibit low sensitivity to environmental conditions such as humidity and temperature
- Allow the manufacture of tablet using conventional processing and packaging equipments.

Advantages of MDT's (Debjit Bhowmik *et al*., 2009; Raghavendra Rao and Upendra Kulkarni, 2010; Dali Shukla *et al*., 2009; Dequeker, 2014): MDT's offer dual advantages of solid dosage forms and liquid dosage forms along with special features which include:

•**Accurate dosing*:*** Being unit solid dosage forms, provide luxury of accurate dosing, easy portability and manufacturing, good physical and chemical stability and an ideal alternative for pediatric and geriatric patients.

•**Enhanced bioavailability:** Bioavailability of drugs is enhanced due to absorption from mouth, pharynx and esophagus.

•**Rapid action:** Fast onset of therapeutic action as tablet gets disintegrated rapidly along with quick dissolution and absorption in oral cavity.

•**Patient compliance:** No need of water to swallow the dosage form. Hence, it is convenient for patients who are traveling and do not have immediate access to water.

•**Ease of administration:** Convenient to administer specially for geriatric, pediatric, mentally disabled and bed ridden patients who have difficulty in swallowing.

•**Obstruction free:** No risk of suffocation in airways due to physical obstruction when swallowed, thus providing improved safety and compliance.

•**Enhanced palatability:** Good mouth feel, especially for pediatric patients as taste masking technique is used to avoid the bitter taste of drug.

•**Simple packaging:** No specific packaging required. It can be packaged in push through blisters.

•**Business avenue:** Provide new business opportunities in the form of product differentiation, line extension, uniqueness and life cycle management.

•**Cost effective:** Conventional processing and packaging equipments allow the manufacturing of tablets at low cost.

Disadvantages (Ellsworth *et al*., 2003; Engelhardt *et al*., 1995)

- Fast dissolving tablet is hygroscopic in nature so must be keep in dry place.
- It requires special packaging for properly stabilization and safety of stable product.
- Some time it possesses mouth feeling

The need for development of MDT's (Furtado *et al*., 2011; Ganesh Kumarudas *et al*., 2010; Hawkey *et al*., 1998; Jacob *et al*., 2007)

Patient factors: Fast dissolving dosage forms are suitable for those patients (particularly pediatric and geriatric patients) who are not able to swallow traditional tablets and capsules with an 8-oz glass of water. These include the following:

- Patients who have difficulty in swallowing or chewing solid dosage form
- Patients incompliance due to fear of choking
- Very elderly patients of depression who may not be able to swallow the solid dosage forms
- An eight-year old patient with allergies desires a more convenient dosage form than antihistamine syrup
- A middle-aged patient undergoing radiation therapy for breast cancer may be too nauseous to swallow her h2-blocker
- A schizophrenic patient who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic
- A patient with persistent nausea, who may be journey, or has little or no access to water.

Effectiveness factor: Dispersion in saliva in oral cavity causes pre-gastric absorption of drug which dissolves. Buccal, pharyngeal and gastric regions are all areas of absorption for many drugs. Any pre-gastric absorption avoids first pass

hepatic metabolism which increase the bioavailability. Furthermore, safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism and for drugs that have a substantial fraction of absorption in the oral cavity and pre-gastric segments of GIT.

Manufacturing and marketing factors: As a drug nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, unique product differentiation, value-added product line extension, and extend patent protection, while offering its patient population a more convenient dosage form. This leads to increased revenue, while also targeting underserved and under-treated patient populations. As examples, Eisai Inc. launched Aricept MDT's, a line extension of donepezil for Alzheimer's disease, in Japan in 2004 and in the U.S. in 2005 in response to a generic challenge filed in the U.S. by Ranbaxy. Merck's Japanese subsidiary launched Lipola M, a line extension of its block-buster, Zocor®, a cholesterol-lowering drug, in response to seventeen generic registrations of simvastatin applied for in Japan in 2004. Marketers build a better brand and in this way company's reputation can be improved.

Challenges in the formulation of MDT's

•**Mechanical strength and disintegration time:** Disintegration time will be delayed if the mechanical strength is strong. So a good compromise between these two parameters is always essential.

•**Taste masking:** Effective taste masking of the bitter drugs must be done so that the taste of the drug is not felt in the oral cavity.

•**Mouth feel:** The particles generated after disintegration of the MDT's should be as small as possible. It should leave minimal or no residue in mouth after oral administration. Moreover addition of flavors and cooling agents like menthol improves the mouth feel.

•**Sensitivity to environmental conditions:** MDT's generally should exhibit low sensitivity to environment conditions such as humidity and temperature.

•**Cost:** The technology adopted for an MDT's should be acceptable in terms of cost of the final product.

Formulation of MDTs: (Jain and Naruka, 2009; Jashanjit Singh *et al*., 2008; Kaushik *et al*., 2004)

•**Bulking materials:** Bulking materials are significant in the formulation of mouth-melting tablets. The material contributes functions of a diluent, filler and cost reducer. Bulking agents improve the textural characteristics that in turn enhance the disintegration in the mouth, besides; adding bulk also reduces the concentration of the active in the composition. The recommended bulking agents for this delivery system should be more sugar-based such as mannitol, polydextrose, lactitol, DCL (direct compressible lactose) and starch hydrolystate for higher aqueous solubility and good sensory perception. Bulking agents are added in the range of 10 percent to about 90 percent by weight of the final composition.

•**Emulsifying agents:** Emulsifying agents are important excipients for formulating mouth-melting tablets they aid in rapid disintegration and drug release without chewing, swallowing or drinking water. In addition, incorporating emulsifying agents is useful in stabilizing the immiscible blends and enhancing bioavailability. A wide range of emulsifiers is recommended for fast-tablet formulation, including alkyl sulfates, propylene glycol esters, lecithin, sucrose esters and others. These agents can be incorporated in the range of 0.05 percent to about 15 percent by weight of the final composition.

•**Lubricants:** Lubricants, though not essential excipients, can further assist in making these tablets more palatable after they disintegrate in the mouth. Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach.

•**Flavours and Sweetners:** Flavours and taste-masking agents make the products more palatable and pleasing for patients. The addition of these ingredients assists in overcoming bitterness and undesirable tastes of some active ingredients.

Superdisintegrants

The Superdisintegrants can be classified into two categories

1. Natural Superdisintegrants
2. Synthetic Superdisintegrants

Natural superdisintegrants: They are natural in origin and are preferred over synthetic substances because they are comparatively cheaper, abundantly available, non irritating and non toxic in nature.

Advantages of natural plant–based materials

•**Biodegradable:** Naturally available biodegradable polymers are produced by all living organisms. They represent truly renewable source and they have no adverse impact on humans or environmental health (e.g., skin and eye irritation).

•**Biocompatible and non-toxic:** Chemically, nearly all of these plant materials are carbohydrates composed of repeating sugar (monosaccharide) units. Hence, they are non- toxic.

•**Low cost:** It is always cheaper to use natural sources. The production cost is also much lower compared with that for synthetic material. India and many developing countries are dependent on agriculture.

•**Environmental-friendly processing:** Gums and mucilage's from different sources are easily collected in different seasons in large quantities due to the simple production processes involved.

•**Local availability:** In developing countries, governments promote the production of plant like guar gum and tragacanth because of the wide applications in a variety of industries.

•**Better patient tolerance as well as public acceptance:** There is less chance of side and adverse effects with natural materials compared with synthetic one. For example, PMMA, povidone.

Disadvantages (Kuccherkar *et al*., 2003; Khalid Abed *et al*., 2010)

•**Microbial contamination**: The equilibrium moisture content present in the gums and mucilages is normally 10% or more and, structurally, they are carbohydrates and during production, they are exposed to the external environment and, so there is a chance of microbial contamination. However, this can be prevented by proper handling and the use of preservatives.

•**Batch to batch variation:** Synthetic manufacturing is a controlled procedure with fixed quantities of ingredients, while the production of gum and mucilages is dependent on environmental and seasonal factors.

•**Uncontrolled rate of hydration:** Due to differences in the collection of natural materials at different times, as well as differences in region, species, and climate conditions the percentage of chemical constituents present in a given material may vary. There is a need to develop suitable monographs on available gums and mucilages.

•**Reduced viscosity on storage**: Normally, when gums and mucilages come into contact with water there is an increase in the viscosity of the formulations. Due to the complex nature of gums and mucilages, it has been found that after storage there is reduced in viscosity.

And this superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

Mechanism of superdisintegrants by swelling

Swelling index of the superdisintegrants is commonly studied in simulated saliva. Volume occupied by the material at the end of 4 h should be noted and swelling index is calculated by the formula.

Swelling Index = [(Final volume - Initial volume)/initial volume)] x 100

Selecting the superdisintegrant (Kei-ichi Koizumi *et al*., 1997; Kuldeepak Sharma *et al*., 2005)

Although the superdisintegrant primarily affects the rate of disintegration, when used at high levels it can also affect mouth feel, tablet hardness, and friability. Thus, several factors must be considered when selecting a superdisintegrant.

a)Disintegration: The disintegrant must quickly wick saliva into the tablet to generate the volume expansion and hydrostatic pressures necessary to provide rapid disintegration in the mouth. Compactability. When manufacturing an ODT, it is desirable to have tablets with acceptable hardness at a given compression force to produce robust tablets that avoid the need to use specialized packaging while maximizing production speed. Thus, a more compactable disintegrant will produce stronger, less-friable tablets.

Table: Examples of natural superdisintegrants in marketed formulations (Kerly *et al*., 2007)

Polymer used	Botanical Name	Drug	Result
Yellow potato starch	*Solanum tuberous*	Rizatriptine benzoate	Fast disintegration
Chitosan	*Shell of crustaceans*	Cinnarzine	Good mouth feel & decreased DT.
Cucurbita maxima powder	*Cucurbita maxima*	Diclofenac sodium	Disintegrating agent
Hibiscus rosa sinensis and treated agar	*Hibiscus rosa sinensis*	Famotidine	Decreased wetting time
Hibiscus rosa sinensis mucilage powder	*Hibiscus rosa sinensis*	Aceclofenac	Decreased disintegration time
Lallemantia raylene seed mucilage	*Lallemantia raylene*	Nimesulide	DT decreases with increase in concentration
Garden cress	*Lepidium sativum*	Nimesulide	Decreased disintegration time
Modified aegle marmelos gum	*Aegle marmelos*	Aceclofenac	Increased solubility
Mango	*Mangifera indica*	Metformin hydrochloride	Better drug release properties
Orange peel pectin	*Citrus sinensis*	Paracetamol	Binding agent
Planatgo ovata, gum karaya, agar	*Plantago ovata, Sterculia urens Gelidium amansii*	Granisetron Hcl	Better disintegrant than synthetic disintegrants

Synthetic superdisintegrants

Superdisintegrant used is the one that effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly. The problem is, it is hygroscopic therefore not used with moisture sensitive drugs.

Table: Examples of synthetic superdisintegrants in marketed formulations

DRUG	SUPERDISNTEGRANTS	METHOD
Carvedilol	Cross povidone, Cross carmellose sodium, Sodium starch glycolate	Direct compression
Valsartan	Cross povidone, Cross carmellose sodium, Sodium starch glycolate	Direct compression
Ziduovudine	B- cyclodextrin, crosspovidone	Direct compression
Ondasetron Hcl	Crosscarmellose sodium, Sodium starch glycolate	Direct compression
Levocetrizine Hcl	Cetric acid, Sodium bicarbonate	Direct compression
Chlorpromazine Hcl	Crosspovidone, Acid-di-sol, Sodium starch glycolate	Direct compression
Reloxifene Hcl	Cross carmellose sodium, Sodium starch glycolate	Direct compression
Terbutaline sulphate	Crosspovidone, Cross carmellose sodium	Direct compression
Disulfuram	Sodium starch glycolate	Dry granulation
Aceclofenac	Acid-di-sol, Sodium starch glycolate	Wet granulation
Lisinopril	Acid-di-sol, Sodium starch glycolate	Wet granulation
Fentanyl citrate	Kollidon CL	Sublingual method
Losartan potassium	Cross carmellose sodium, Sodium starch glycolate	Direct compression

b)Mouth feel: To achieve patient compliance, MDT's must provide a palatable experience to the patient. Large particles can result in a gritty feeling in the mouth. Thus, small particles are preferred. If the tablet forms a gel-like consistency on contact with water, however, it produces a gummy texture that many consumers find objectionable.

c)Flow: As with all direct-compression tablet formulations, attaining good flow and content uniformity is important to achieving the required dosage per unit. In typical tablet formulations, superdisintegrants are used at 2-5 wt. % of the tablet formulation. With MDT formulations, disintegrant levels can be significantly higher. At these higher use levels, the flow properties of the disintegrant are more important because it makes a greater contribution to the flow characteristics of the total blend.

d)Taste-masking agents: Taste masking of drug may be achieved with preventing the exposure of drug to the tongue through processing or adding competing taste-masking agents. Exposure of solubilized drug to the oral cavity can be prevented by encapsulation in polymer systems or complexation.

The approaches are as follows

- Layering the drug onto inert beads using a binder followed by coating with a taste-masking polymer.
- Granulating the drug and coating with a taste masking polymer.
- Spray drying the drug dispersed or dissolved in a polymeric solution to get taste-masked particles.
- Complexation by the use of inclusion in cyclodextrins.
- Psychological modulation of bitterness.
- Coacervation to form microencapsulated drug within a polymer.
- Formation of pellets by extrusion spheronization.

e)Sweeteners: Sucrose and other natural sweeteners, such as sorbitol, can be used in effervescent products, although artificial sweetening agents are customary. However, the application of artificial sweeteners is restricted by health regulations. Saccharin or its sodium and calcium salts are used as sweeteners. Aspartame is also employed as a sweetener in effervescent tablets. Earlier, cyclamates and cyclamic acid were the artificial sweeteners of choice, but their use has now been restricted. Some commonly used sweeteners are:

Example: Sorbitol, Mannitol, Maltitol solution, Maltitol, Xylitol, Erythritol, Sucrose, Fructose, Maltose, aspartame, Glycerin, sugars derivatives etc.

f)Binders: Main role of Binders is to keep the composition of these fast melting tablets together during the compression stage. Binders can either be liquid, semisolid, solid or mixtures of varying molecular weights such as polyethylene glycol. The right selection of a binder or combination of binders is essential to maintain the integrity and stability of the tablet. The temperature of the excipient should be preferably around 30–350C for faster melting properties. Further, its incorporation imparts smooth texture and disintegration characteristics to the system.

Example: Binders commonly used are cellulosic polymers such as ethylcellulose, hydroxypropylcellulose (HPC), and hydroxypropylmethylcellulose (HPMC), alone or in admixtures povidones, polyvinyl alcohols, and acrylic polymers. Acrylic polymers used are the ammoniomethacrylate copolymer, polyacrylate, and polymethacrylate.

g)Lubricants: Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach. Example: Magnesium stearate, stearic acid, leucine, sodium benzoate, talc, magnesium lauryl sulphate, liquid paraffin etc.

h)Flavours: Peppermint flavour, clove oil, anise oil, eucalyptus oil. Flavoring agents include, vanilla, citrus oils, fruit essences etc.

i)Fillers: Directly compressible spray dried Mannitol, Sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium phosphate, pregelatinized starch, magnesium trisilicate, aluminium hydroxide etc.

j)Surface active agents: sodiumdoecylsulfate, sodium laurylsulfate, Tweens, Spans, polyoxyethylene stearate

Mechanism of tablet disintigrants: The tablet breaks to primary particles by one or more of the mechanisms listed below.

a. By capillary action
b. By swelling
c. Because of heat of wetting
d. Due to disintegrating particle/particle repulsive forces
e. Due to deformation
f. Due to release of gases
g. By enzymatic action

a. By capillary action

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug/excipient and on tabletting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

b. By swelling

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

c. Because of heat of wetting

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation,

however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

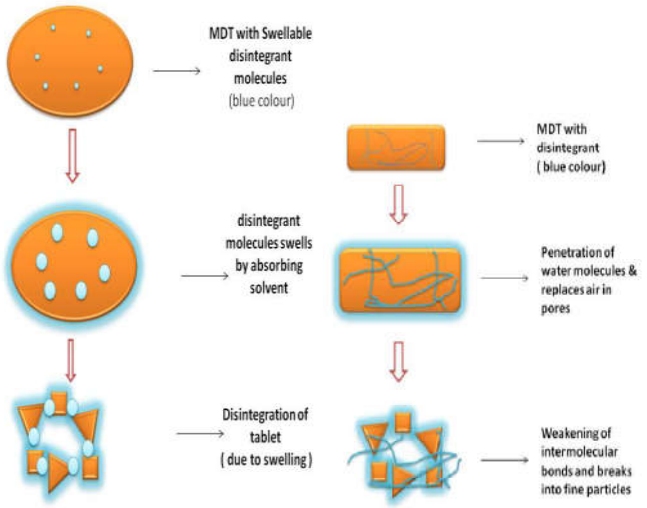


Fig: Disintegration of tablet by wicking and swelling

d. Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

e. Due to deformation

Hess had proved that during tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet.

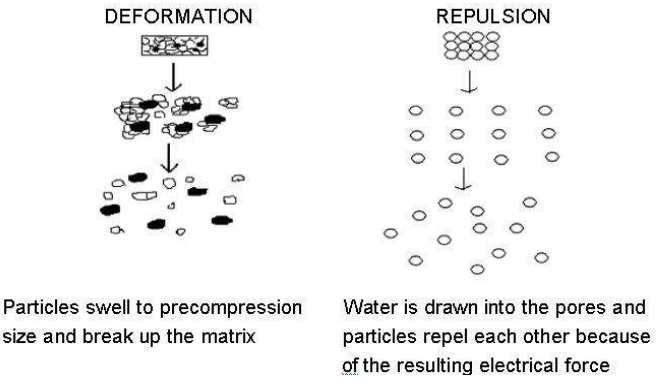


Fig: Disintegration by deformation and repulsion

f. Due to release of gases

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

e. By enzymatic reaction: Here, enzymes presents in the body act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration.

Table: Dintegrating Enzymes

Enzymes	Binder
Amylase	Starch
Protease	Gelatin
Cellulase	Cellulose and its derivatives
Invertase	Sucrose

Table: List of superdisintegrants (Lailla and Sharma, 1993)

Superdisintegrants	Example	Mechanism of action	Special comment
Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose® Solutab®	Crosslinked cellulose	Swells 4-8 folds in < 10 seconds. Swelling and wicking.	Swells in two dimensions. Direct compression or granulation starch free.
Crospovidone Crospovidon M® Kollidon® Polyplasdone®	Crosslinked PVP	Swells very little and returns to original size after compression but act by capillary action.	Water insoluble and spongy in nature so get porous tablet.
Sodium starch glycolate Explotab® Primogel®	Crosslinked starch	Swells 7-12 folds in <30 seconds.	Swells in three dimensions and high level as sustain release matrix.
Alginic acid NF Satialgine®	Crosslinked alginic acid	Rapid swelling in aqueous medium or wicking action.	Promote disinter-gration in both dry or wet granulation.
Calcium silicate		Wicking action	Highly porous, light weight.

Co-processed Excipients: New and improved superdisintegrants continue to be developed to meet the needs of advanced tablet manufacturing. It requires the development of various added functionality excipients, which are used to achieve formulations with desired end effects. Until now only superdisintegrants are available to prepare the dosage forms, but now days different blend of excipients are available which can give disintegration property. Some co-processed excipients blends are designed to satisfy the need of more than one excipient.

Co-processed blends of excipients: It involves the mixture blend of more than two excipients to satisfy the required quality using different technique like spray drying and freeze drying etc.

Cardiac arrhythmias: The heart rate is normally determined by intrinsic impulses generated in the SA node. The rhythm is determined by the route of impulse transmission through the conducting system.

Conventional techniques for MDT's

Table: Conventional techniques for MDT's

S. No	Techniques	Method and characteristics of prepared MDT's
1	Disintegrant addition	The basic principle involved in formulating Fast disintegrating tablets by disintegrates addition technique is addition of superdisintegrants in optimum concentration so as to achieve mouth dissolving along with the good mouth feel. Sodium starch glycolate, crospovidone and crosscarmellose are some of the popular superdisintegrants. Characteristics: Similar to conventional tablets with higher % of disintegrants, lower hardness and higher % of friability.
2	Freeze Drying or Lyophilization	Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biological at low temperature under conditions that allow removal of water by sublimation. The drug is dissolved or dispersed in an aqueous solution of a carrier. The mixture is poured into 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. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. Characteristics: The preparations are highly porous, have high specific surface area, dissolve rapidly and ultimately show improved absorption and bioavailability.
3	Tablet Molding	In this method, molded tablets are prepared by using water soluble ingredients so that the tablets dissolve completely and rapidly. The powder blend is moistened with a hydroalcoholic solvent and is molded into tablets under pressure lower than that used in conventional tablet compression. The solvent is then removed by air drying. Characteristics: Molded tablets are very less compact than compressed tablets. These possess porous structure that enhances dissolution.
4	Sublimation	Inert solid ingredients that volatilize rapidly like urea, camphor ammonium carbonate, ammonium bicarbonate, hexamethylene tetramine) were added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials were then removed via sublimation, which generates porous structure. Characteristics: Porous structure that enhances dissolution by using volatile material or solvent e.g. cyclohexane, benzene etc.
5	Spray-Drying	The formulations are incorporated by hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or crosscarmellose sodium as disintegrating and an acidic material (e.g. citric acid) and or alkali material (e.g. sodium bicarbonate) to enhance disintegration and dissolution. Characteristics: Prepared tablet disintegrates within 20 seconds when immersed in an aqueous medium.
6	Direct Compression (Luca Dobetti, 2001)	Direct compression method is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Characteristics: It is most cost effective tablet manufacturing technique.
7	Mass-Extrusion	This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using 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 tablets. Characteristics: The dried product can be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.
8.	Cotton candy process	Involves the formation of matrix of polysaccharides by simultaneous action of flash melting and spinning. This candy floss matrix is then milled and blended with active ingredients and excipients after re-crystallization and subsequently compressed to MDTs. Characteristics: It can accommodate high doses of drug and offers improved mechanical strength
9	Nanonization	Involves size reduction 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. Characteristics: It is used for poorly water soluble drugs. It leads to 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).
10	Compaction a)Melt granulation b)Phase-transition process	Prepared by incorporating a hydrophilic waxy binder (super polystate) PEG-6-stearate. Super polystate not only acts as binder and increase physical resistance of tablet but also helps the disintegration of tablet. Characteristics: It melts in the mouth and solubilizes rapidly leaving no residue. Prepared by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. The tablet hardness was increased after heating process due to increase of inter particle bond induced by phase transition of lower melting point sugar alcohol. Characteristics: The compatibility increased and so sufficient hardness gained by the formulation.
11	Fast Dissolving Films	A non-aqueous solution is prepared containing water soluble film forming polymer drug and other taste masking ingredients are used to form a film after evaporation of solvent. In case of a bitter drug, resin adsorbate or coated micro particles of the drug can be incorporated into the film. Characteristics: The thin films size less than 2X2 inches, dissolution in 5 sec, instant drug delivery and flavored after taste.

Table: Description and Applications of Co-processed Excipients (Mona Nagar *et al*., 2009)

Grade	Description	Applications
Ludiflash	Have mild sweet taste and cooling effect in the mouth. Have superior flowability and low hygroscopicity. Does not dissolve completely in water or organic solvents.	Excellent excipient for direct compression of fast-disintegrating solid oral dosage forms for rapid release.
F-melt	Highly flowable with spherically dense particles, disintegration time within 30 seconds, time-saving and cost-effective, less sticking or capping.	Suitable for direct compre ssion manufacturing of fast-dissolving oral tablets containing APIs and lubricants.
Pharmaburst	Easy-to-use quick dissolving delivery platform, it is smooth and creamy and is highly compatible.	Gives flexibility to develop robust "Quick Dissolve" formulations in-house, at a reasonable cost.
Modified chitosan with silicon dioxide	Water wicking and swelling properties with improved flow and compaction properties.	Acts as superdisintegrant and filler.
Pearlitol SD	Spheronised granulated mannitol Pearlitol® 100SD, mean diameter: 100 µm Pearlitol® 200SD, mean diameter: 180 µm Sweetening power about 40% that of sucrose.	Excellent excipient for direct compression especially for chewable and effervescent tablets.
Mannogem EZ	Excellent compressibility due to its open crystal-line structure. Sweetening power about 50% that of sucrose.	Quick dissolve application and an excellent carrier for active moieties which are sensitive to hydrolysis.
Polacrilin Potassium	No lump formation after disintegration. High compatibility with excipients and common therapeutic agent.	Used as a tablet disinter- grant and as a taste-masking agent for various drugs.
Glucidex IT	Free-flowing due to fewer fine particles, quick dispersion, and quick dissolution.	Used as diluent for tablet, capsule, spray drying carrier, direct compression maltodextrin which would be used for directly compressible formulation of vitamins and supplement tablets.

Table: Promising Drugs to be incorporated In Mouth dissolving tablets (Mohamed Hassan *et al*., 2006)

S.No.	Therapeutic activity	Drugs used
1	Analgesic and Anti- inflamatory agents	Piroxicam, Nabumetone, Ibuprofen, Oxypenbutazone, Oxaprozin, Meclofenamic Acid, Fenbufen, Aloxiprin.
2	Antihelmintics	Hydroxl Napthoate, Thiabendazole, Mebendazole, Praziquantel, Pyrantel, Ivermectin, Cambendazole, Albendazole
3	Antiarrhythmic agents	Vanidine Sulphate, Flecainite Acetate, Disopyramide, Amidarone Hcl
4	Antibacterial agents	Trimethorprim, Sulphapyridine, Sulphabenzamide, Sulphadoxine, Pencillin, Banethamine, Ethioniamide, Nitofurantoin, Doxycycline, Cloxacillin, Clofazimine, Cinoxicam.
5	Anticoagulants	Nicoumalaone, Phenindione, Dipyrimidine, Dicoumarol
6	Antidepressant	Maprotiline Hcl, Trimipramine Maleate, Tradazone Hcl, Mianserin Hcl, Ciclazindol, Amoxapine.
7	Antidaibetics	Tolbutamide, Glipizide, Gliclazide, Glibencamide, Chlorpropamide, Acetohexamide
8	Antiepileptics	Methylphenobarbitone, Oxycarbazepine, Phenytoin, Sulthiame, Phenobarbitone, Phenacemide, Methion, Clonazepam
9	Antifungal	Itraconazole, Tioconazole, Terconazole, Amphitericin, Natomycin, Griseofulvin, Flucytocine, Clotrimazole
10	Antimalarial	Mefloquine, Chloroquine, Pyramethamine, Choloroproguanil Hcl, Amodiaquine
11	Antimusacarinic agents	Tropecamide, Oxyphencyclamine Hcl, Hyoscyamine, Biperdine, Atropine
12	Antiprotozoal agents	Tinidazole, Benznidazole, Metronidazole, Diloxamidefuroate, Clioquinol
13	Anxiolytics, sedatives, hypnotics and neuroleptics	Droperidol, Flurazepam, Ethinamate, Diazepam, Bromperidol, Clozapin, Bromazepam, Bentazipam, Barabitone, Alprazolam.
14	Cardiac inotropic agents	Enoximone, Medigoxin, Digoxin, Digitoxin, Amrinone
15	Antiparkinsonian agents	Ysuride Maleate, Mesylate, Bromocriptine
17	Anti thyroid agents	Carbimazole, Propylthiouracil.
18	Lipid Regulating Agents	Bezafibrate, Clofibrate, Fenofibrate, Gemfibrozil, Probucol.

The heart rate is usually measured as the pulse, but to determine the rhythm, an electrocardiogram (ECG) is required. "A cardiac arrhythmia is any disorder of heart rate or rhythm, and is the result of abnormal generation or conduction of impulses". The normal cardiac cycle gives rise to normal sinus rhythm, which has a rate between 60 and 100 beats per minute.

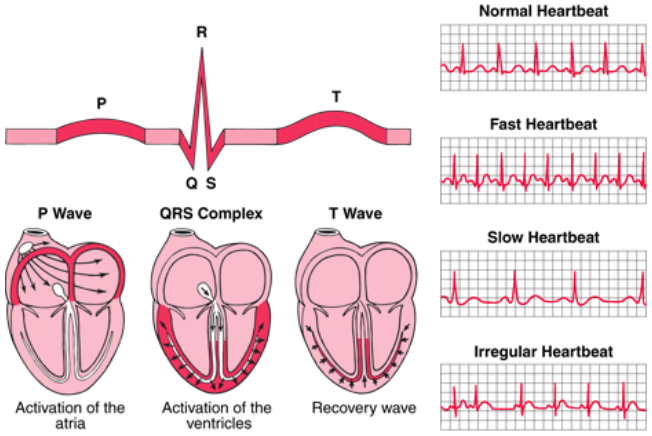


Fig: Cardiac arrthymias

Types of cardiac arrhythmias

a)Sinus Bradycardia: This is normal sinus rhythm below 60 beats per minute. This may occur during sleep and is common in athletes. It is an abnormality when it follows myocardial infraction or accompanies raised intracranial pressure. Myocardial infraction may occur when a branch of a coronary artery is occluded. The commonest cause is an athermanous plaque complicated by thrombosis.

b)Sinus Tachycardia: This is normal sinus rhythm above 100 per minute when the individual is at rest. This accompanies exercise and anxiety, but is an indicator of some disorders, e.g. fever, hyperthyroidism, some cardiac conditions.

c)Asystole: This occurs when there is no electrical activity in the ventricles and therefore no cardiac output. The ECG shows a flat line. Ventricular fibrillation and a systole cause sudden and complete loss of cardiac output, i.e. cardiac arrest and death.

d)Fibrillation: This is the contraction of the cardiac muscle fibers in a disorderly sequence. The chambers do not contract as a coordinated unit and the pumping action is disrupted. In atrial fibrillation, contraction of the atria is uncoordinated and rapid, pumping is ineffective and stimulation of the AV node is disorderly. Ventricular contraction becomes rapid and rhythm and force irregular; although an adequate cardiac output and blood pressure may be maintained, the pulse is irregular. The cause of increased excitability and disorganized activity are not always clear but predisposing conditions include:

1. Ischemic heart disease
2. Degenerative changes in the heart due to old age
3. Thyrotoxicosis
4. Rheumatic heart disease.

Ventricular fibrillation is a medical emergency that will swiftly lead to death if untreated, because the chaotic electrical activity within the ventricular walls cannot coordinate effective pumping action. Blood is not pumped from heart into either the pulmonary or the systemic circulation. No impulse can be felt; consciousness is lost and breathing stops. The ECG shows an irregular chaotic trace with no recognizable wave pattern.

e) Heart Block: Heart block occurs when normal impulse transmission is blocked or impaired. A common form involves obstruction of impulse transmission through the AV node is involved, but conducting tissue in atria or ventricles may also be affected.

Antiarrhythmic drugs: Ant arrhythmic drugs are used to correct cardiac arrhythmias. Cardiac arrhythmias occur as a result of defective impulse formation or defective impulse conduction/transmission.

Classification of Ant arrhythmic drugs

I. **Myocardial depressants:** Quinidine, Procainamide, Disopyramide, Lignocaine, Phenytoin.

II. **Sympathetic blockers:** propnolol.
III. **Calcium channel blockers:** Verapamil
IV. **Miscellaneous:** Amiodarone, Aprindine.

Amiodarone: It is structurally related to thyroxin. It has an ant adrenergic effect. It acts by prolonging effective refractory period and ventricular duration of action potential. It is the drug of choice in refractory ventricular and supraventricular tachycardia.

Adverse reaction: nausea anorexia. Corneal opacities and hallucinations.

Review of literature

Past work on mouth dissolving tablets

- Jashanjit *et al*. (2010) Optimization Studies on Design and Evaluation of Orodispersible Pediatric Formulation of Indomethacin formulated by non-aqueous wet granulation using Cros-Povidine (5%w/w) & mannitol (44%w/w) shows fast drug release rate of 99.5% within 30 min.
- Kawano *et al*. (2009) investigated the masking of the taste of furosemide (FU). The taste was masked well when granules were prepared by the mixing & mixing/coating methods. Tablets were prepared from these granules with mannitol & crystalline cellulose added as fillers.
- Furtado *et al*. (2008) prepared oro dispersible tablets of famotidine by using camphor as sublimating agent & sodium starch glycolate together with cros-carmellose sodium as superdisintegrant. All the formulations showed low weight variation with dispersion time less than 30 sec & rapid in-vitro dissolution. The optimized formulation showed good release profile with maximum drug being released at all time intervals.
- Ahmed *et al*. (2007) developed a fast-disintegrating lyophilized dry emulsion (LDE) tablets that enhances the in-vitro dissolution & in-vivo absorption of griseofulvin. Development of a fast-disintegrating lyophilized dry emulsion (LDE) tablet that enhanced the in vitro dissolution and in vivo absorption of griseofulvin is presented. The LDE tablets were prepared by freeze-drying o/w emulsions of GF, a drug for which bioavailability is known to be enhanced by fat co-administration. Oil-in-water emulsions were prepared using a gelatin solution (2%, w/v) as the water phase and medium chain triglycerides (Miglyol) or sesame oil as the oil phase. In addition, different emulsifiers were evaluated.
- Anand *et al*. (2007) prepare taste masked oro solvent evaporation method using acetone as solvent for pH-sensitive polymer & light liquid paraffin as the encapsulating medium. Effective taste-masking was achieved for PDL using the technique of microencapsulation & ODTs of acceptable characteristics were obtained by disintegrant addition & direct compression (Jain and Naruka, 2009).
- Mohamed *et al*. (2006) reported Meloxicam solid dispersions with PEG 6000 (350mg) & SLS (75mg) by solvent evaporation method. They used lactose (3g) & MCC (4:1) as additives. The increase in bioavailability of Meloxicam is observed with solid dispersion technique this may be due to the increase wettability & hydrophilic nature of the carrier.
- Kuno *et al*. (2005) prepared & evaluated rapidly disintegrating (RD) tablets manufactured by phase transition of sugar alcohols. Tablets were prepared by compressing the powder erythritol (M.P 122^0C) & xylitol (M.P 92-95^0C) then heating at about 93^0C for 15 min. Hardness & disintegration time of the heated tablets increased with an increase of the xylitol content.
- Kerly *et al*. (2005) developed & evaluated of amoxicillin formulation by direct compression. They studied the type of MCC (avicel PH 102/ avicel PH 200), the presence are absence of spray dried lactose, & the presence or absence of the superdisintegrating agent cros-carmellose sodium. With avicel PH 102 & superdisintegrating agent shows good result.
- Sameer *et al*. (2005) Effects of disintegration-promoting agent, lubricants and moisture treatment on optimized fast disintegrating tablets. Effects of calcium silicate (disintegration-promoting agent) and various lubricants on an optimized cyclodextrin-based fast-disintegrating tablet formulation were investigated. Effects of moisture treatment were also evaluated at 75, 85 and 95% relative humidities. A two factor, three levels (32) full factorial design was used to optimize concentrations of calcium silicate and lubricant.
- Viral Shah, Rucha patel studies on mucilage from hibiscus rosasinensis linn as oral disintegrant. The present study was undertaken to separate mucilage from leaves of Hibiscus rosasinensis and explore its use as tablet disintegrant. Dispersible tablets of Aceclofenac were prepared and compared with different concentrations viz; 2, 4, 6 and 8 %(w/w) of Hibiscus rosasinensis mucilage powder and Ac□Di□Sol®. Eight formulations were prepared and evaluated for physical parameters such as thickness, hardness, friability, weight variation, drug content, disintegration time and drug dissolution.
- Monanagar, Sanjay K Singhai, Vikram Chopra, Kishor mandage, formulation, evaluation and comparision of fast-dissolving tablet of nimesulide by using Cros-Povidine as superdisintegrant were prepared by direct compression method. The study was performed by incorporating the superdisintegrant (Cros-Povidine) in 2, 4 %, 8 %, 12 % concentration respectively. Four formulations were prepared to assess their efficiency. The optimized batch was compared with the available marketed preparation .The optimize batch showed excellent in vitro/in vivo dispersion time and drug release as compared to marketed preparation.
- Sudhir Bhardwaj, Vinay Jain, Jat, Ashish mangal, Suman Jain, formulation and evaluation of fast dissolving tablet of Aceclofenac. The poor aqueous solubility of the drug results in variable dissolution rate and hence poor bioavailability. In the present study, an attempt had been made to prepare fast dissolving tablets of the drug using various super disintegrates sodium starch glycolate following by direct compression technique. All the formulation showed disintegration time in range of 12.2 to 27.5 second along with rapid in vitro dissolution.
- Narmada GY, Mohini K, Prakash Rao B, Gowrinath, kumar, Formulation, Evaluation and Optimization of Fast Dissolving Tablets Containing Amlodipine Besylate by Sublimation Method. The results obtained

showed that the quantity of starch potato, sodium starch glycolate, camphor significantly affect response variables. The results indicate that the optimized tablet formulation provides a short DT of 8 sec with sufficient crushing strength and acceptable friability. Stability studies of optimized formulation revealed that formulation is stable.

- B.S.Venkateswarlu, R.Margret Chandira, Talele Ajay, Debjit Bhowmik, Chiranjib, Jayakar, Sampath kumar, formulation development and evaluation of fast dissolving tablets of carvedilol in the present work solubility was enhanced by using β- cyclodextrin as a complexing agent. Sweeteners and flavors were used to enhance the organoleptic properties of tablet. All the formulations were evaluated for the influence of disintegrates and their concentrations on the characteristics of fast dissolving tablets mainly in terms of disintegration time and dissolution studies. Optimized formulation of Ac-Di-Sol Superdisintegrant in the concentration of (6mg) i.e. F3 batch gives best results than all the formulation.
- Rakesh P. Patel, Jagrut H. Dhruv, Bnkimchandra J. Bhatt Ajay. M. Suthar formulation development and optimization of cefditoren pivoxil. In preliminary study different superdisintegrant cros-carmellose sodium (CCS), sodium starch glycolate (SSG) and Cros-Povidine. Microcrystalline cellulose: low□substituted hydroxypropyl cellulose ratio was optimized 8:2 in whole experiment as it gives minimum disintegration time. Full factorial designs 32 was used to optimize concentration of superdisintegrant (X1) and SLS (X2) which were selected as independent variables, and friability, disintegration time and % CDR was selected as dependent variable. From response surface plot of disintegration time, % drug release after 15 minis (*Q15*) and friability it was found that lower disintegration time of tablets could be obtained when X1 and X2 are kept at optimum level.
- Ganesh kumar Gudas, B.Manasa, V.V.Rajesham, S.Kiran kumar, J.Prasanna kumari. Formulation and evaluation of fast dissolving tablets of chlorpromazine hcl, prepared with five Superdisintegrants eg: Sodium starch glycolate, Cros-Povidine, Cros-carmellose, L-HPC, Pregelatinised starch, The blend was examined for angle of repose, bulk density, tapped density, compressibility index and hausners ratio. The tablets were prepared with five superdisintegrant eg: Sodium starch glycolate, Cros-Povidine, Croscarmellose, L-HPC, Pregelatinised starch. The tablets were evaluated for hardness, friability, disintegration time, dissolution rate, drug content, and were found to be within 1 min.
- D.Nagendrakumar, Raju S.A .S.B.Shirsand and M.S.ParaSingh, Design of Fast co-processed Superdisintegrants consisting of Cros-Povidine and sodium starchglycolate in the different ratios (1:1, 1:2 & 1:3). The angle of repose of the developed excipients was found to be < 25, Carr's index in the range of 10-15% and Hausner's ratio in the range of 1.11-1.14. Based on *in vitro* dispersion time (approximately 20 sec), promising formulation CP1 was tested for *in vitro* drug release pattern in pH 6.8 Phosphate buffer and short-term stability (at 400C/75% RH for 3 months), drug excipients interaction (IR spectroscopy) were studied.
- Pankaj P, Amrutkar, Sanjay B. Patil, Abhijeet N, Todarwal, Manoj A. Wagh1, Parag D. Kothawade1, Rajendra K. Surawase, Design and evaluation of taste masked chewable dispersible tablet of lamotrigine by melt granulation work under taken, an attempt was made to mask the taste and to formulate into a chewable dispersible tablet by complexation with Precirol ATO-05, which also acts as taste masking agent. Since, these tablets can be swallowed in the form of dispersion; it is suitable dosage form for paediatric and geriatric patients. Drug-Precirol ATO-05 was prepared in drug to Precirol ATO-05 ratio of 1:2, 1:1.5, 1:1, 1:0.5.
- Ashok Kumar A. G. Agrawal, Indion 414 as superdisintegrant in formulation of melt in mouth Meloxicam tablets. Indion 414 is a high-purity pharmaceutical grade ion exchange resin and is safe for oral consumption, cost-effective and is easily available. The present work was aimed to formulate and evaluate efficacy of Indion 414 as superdisintegrant in formulation of melt in mouth Meloxicam tablets. FTIR spectra of Meloxicam and Indion 414 was obtained to study the compatibility.
- Keichi Koizumi, Yoshiteru Watanabe, Kumiko Morita, Naoki Utoguchi, Mitsuo Matsurnoto, Compressed tablets of a water-soluble material, prepared using mannitol, did not rapidly dissolve in water since it is difficult for water to penetrate into the tablets due to their low porosity. To increase the porosity of the tablets which are prepared by direct compression using mannitol, we developed a novel method whereby camphor, a subliming material, is removed by sublimation from compressed tablets prepared using a mixture of mannitol and camphor. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 sec in saliva in the mouth.

Aim, Objective and plan of work

Aim of work

The aim of present work is to formulate and evaluate fast dissolving tablets of Amiodarone hydrochloride using natural super disintegrants.The antiarrhythmic effect of amiodarone may be due to at least two major actions. It prolongs the myocardial cell-action potential (phase 3) duration and refractory period and acts as a noncompetitive a- and b-adrenergic inhibitor. Amiodarone has attaining various problems like difficulty in swallowing, less bio availability, first pass metabolism in conventional dosage forms. The oral bioavilability of amiodarone can be enhanced by decreasing its extent of first pass effect. This can be achieved by the fast dissolving tablet approach where the drug is get released in oral cavity itself, there by which reduces the first pass effect. Fast dissolving tablets can be prepared by various techniques in which usage of super disintigrants are necessary, which helps in fast disintegration. Various types of super disintigrants are available among them synthetic super disintigrants plays a major role, but the Long term use of the synthetic superdisintegrants causes toxicity which can be suppressed by the natural ones. The swelling efficiency of the natural polymers is responsible for the quick disintegration and quick drug release. Hence, in the present study an attempt has been made to formulate fast dissolving tablets of Amiodarone hydrochloride by using natural superdisintegrants by direct compression technique.

Objective

Need for the study

The concept of mouth dissolving drug delivery system emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and hard gelatin capsules. Hence, they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult.Such problems can be resolved by means of mouth dissolving tablets when put on tongue these tablets disintegrate and dissolve rapidly in saliva without need of drinking water. The faster the drug disintegrates in to solution, the quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. Hence, in the present study an attempt will be made to formulate mouth dissolving tablets of Amiodarone, with a view to develop a convenient means of administration to those patients suffering from difficulties in swallowing.

Objectives of the study

1. Preparation of mouth dissolving tablets of Amiodarone by direct compression using different concentration of Superdisintegrants like sodium starch glycolate (Explotab) and Guargum.
2. Mouth dissolving tablets of Amiodarone were also prepared by using sodium starch glycolate (Explotab) and guargum as superdisintegrants.
3. Mouth dissolving tablets of Amiodarone were evaluated for hardness, friability, weight variation, disintegration time, drug content, water absorption ratio, water absorption time, drug-excipients interaction studies (IR spectroscopy).
4. Study *invitro*dissolution of Amiodarone from the formulated mouth dissolving tablets.

Plan of research work: The proposed present research work was planned as follows:

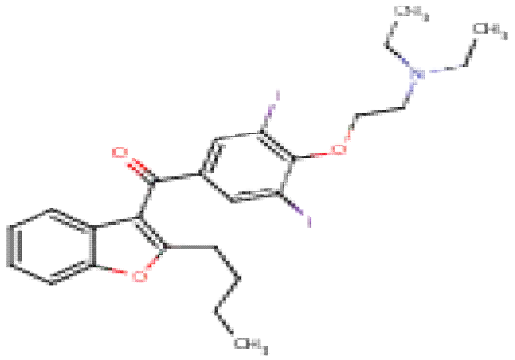
I. Literature survey
II. Selection of drug and excipients.
III. Characterization of excipients and drug substances and their compatibility studies.
IV. Preformulation studies
- Solubility
- Melting point
- Determination of λmax
- Preparation of standard calibration curve of amiodarone hydrochloride.

Pre-compression parameters
- Bulk density
- Tap density
- Carr's index
- Angle of repose
- Haunser ratio

V. Formulation design of fast dissolving tablets of amiodarone hydrochloride by direct compression method using different superdisintegrants in different concentrations.
VI. Comparison of two natural superdisintegrants and selection of optimized formula.
VII. Release kinetics
VIII. Short term stability studies of optimized formulation as per ICH guidelines.

Drug profile (Manoj Ashok Wagh *et al*., 2010)

•**Name**: Amiodarone
•**IUPACName**:(2-{4-[(2-butyl-1-benzofuran-3-yl)carbonyl]-2,6-diiodophenoxy}ethyl)diethylamine.
•**Molecular weight**: 645.3116
•**Chemical Formula**: $C_{25}H_{29}I_2NO_3$
•**Molecular Structure**:



•**Categories**: Anti-Arrhythmia Agents, Vasodilator Agents, Enzyme Inhibitors.

•**Appearance**: A fine white to almost white powder.

•**Melting Point**: 156^0 c

•**Solubility**: It is freely soluble in methanol and dimethylsulfoxide, sparingly soluble in water and ethanol, slightly soluble in ethyl acetate and insoluble in heptanes.

•**Mechanism of action**: The antiarrhythmic effect of amiodarone may be due to at least two major actions. It prolongs the myocardial cell-action potential (phase 3) duration and refractory period and acts as a noncompetitive a- and b-adrenergic inhibitor.

Pharmacology

Pharmacodynamics: Amiodarone belongs to a class of drugs called Vaughan-Williams Class III antiarrhythmic agents. It is used in the treatment of a wide range of cardiac tachyarhthmias, including both ventricular and supraventricular (atrial) arrhythmias. After intravenous administration in man, amiodarone relaxes vascular smooth muscle, reduces peripheral vascular resistance (afterload), and slightly increases cardiac index. Amiodarone prolongs phase 3 of the cardiac action potential. It has numerous other effects however, including actions that are similar to those of antiarrhythmic classes Ia, II, and IV. Amiodarone shows beta blocker-like and calcium channel blocker-like actions on the SA and AV nodes, increases the refractory period via sodium- and potassium-channel effects, and slows intra-cardiac

conduction of the cardiac action potential, via sodium-channel effects. The antiarrhythmic effect of amiodarone may be due to at least two major actions. It prolongs the myocardial cell-action potential (phase 3) duration and refractory period and acts as a noncompetitive a- and b-adrenergic inhibitor.

Pharmacokinetics

•**Absorption**: Slow and variable (about 20 to 55% of an oral dose is absorbed).

•**Volume of distribution**: 12 L/kg

•**Protein binding** : >96%

•**Metabolism**: Amiodarone is extensively metabolized in the liver via CYP2C8 (under 1% unchanged in urine), and can effect the metabolism of numerous other drugs. The major metabolite of amiodarone is desethylamiodarone (DEA), which also has antiarrhythmic properties. The metabolism of amiodarone is inhibited by grapefruit juice, leading to elevated serum levels of amiodarone.

•**Elimination**: Amiodarone is eliminated primarily by hepatic metabolism and biliary excretion and there is negligible excretion of amiodarone or DEA in urine.

• **Half life** : 58 days (range 15-142 days)

• **Clearance**: 90-158 mL/h/kg [Healthy with a single dose IV (5 mg/kg over 15 min)]

100 mL/h/kg [Normal subjects > 65 yrs]
150 mL/h/kg [younger subjects]
220 and 440 mL/h/kg [patients with VT and VF]

•**Toxicity:** Intravenous, mouse: LD_{50} = 178 mg/kg. Some side effects have a significant mortality rate: specifically, hepatitis, exacerbation of asthma and congestive failure, and pneumonitis.

•**Therapeutic use:** Antiarrhythmtic drugs are used to treat the disorders of heart rhytham.

Excipient profile

Sodium Starch Glycolate

Synonyms: Carboxymethyl starch, Explotab, Primogel.

- **Functional Category:** Tablet and Capsule disintegrant.
- **Description:** White to off-white, odorless, tasteless, free-flowing powder.
- **Solubility:** Practically insoluble in water, sparingly soluble in ethanol (95 %). Inwater it swells upto 300 times its volume.
- **Stability:** It is a stable material.

Incompatibilities: Incompatible with Ascorbic acid.

Safety: It is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may be harmful.

Applications: As a disintegrant in tablet (wet granulation and direct compression) and capsules formulations in 2-8 % concentration.

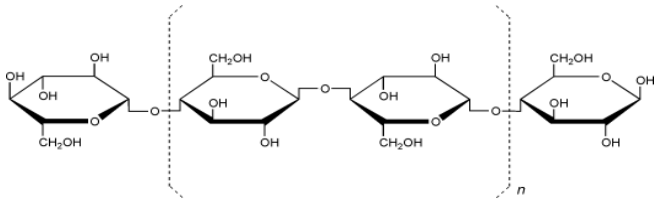
Storage conditions: It should be stored in a well-closed container to protect from wide variations in humidity and temperature that may cause cracking.

Microcystalline cellulose (Rakesh P. Patel *et al*., 2010)

Nonproprietary Names

IP: Microcrystalline cellulose
BP: Microcrystalline cellulose
PhEur : Cellulosum microcristallinum
USPNF: Microcrystalline cellulose
Synonyms: Avicel PH, Celex, Cellulose gel, Cephere, Ceolus KG.

Structural formula



Description: Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Functional Category: Adsorbent, Suspending agent, as a diluent in tablets & capsules, tablet disintegrant.

Solubility: Practically insoluble in water.

Stability and storage conditions: Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Applications in Pharmaceutical Formulation or Technology: Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrates properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products.

TALC

Nonproprietary Names

IP: Talc
BP: Purified talc
PhEur: Talcum
USPNF : Talc

Synonyms: Altalc, hydrous magnesium calcium silicate, hydrous magnesium silicate, magnesium hydrogen metasilicate, Magsil Osmanthus, Magsil Star, powdered talc.

Description: Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres

readily to the skin and is soft to the touch and free from grittiness.

Functional Category: Anticaking agent, glidant, tablet and capsule diluent, tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology: Talc was once widely used in oral solid dosage formulations as a lubricant and diluent.

Stability and Storage Conditions: Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation.

Safety: Talc is used mainly in tablet and capsule formulations. Talc is not absorbed systemically following oral ingestion and is therefore regarded nontoxic material.

Magnesium stearate (Suhas M. Kakade *et al*., 2010)

Nonproprietary Names

IP: Magnesium Stearate
BP: Magnesium Stearate
PhEur: Magnesii Stearas
USPNF: Magnesium Stearate

Synonyms: Magnesium octadecanoate; octadecanoic acid, magnesium salt.

Chemical name: Octadecanoic acid magnesium salt

Functional Category: Tablet and capsule lubricant

Description: Magnesium Stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Solubility: Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Applications in Pharmaceutical Formulation or Technology: Magnesium Stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w.

Aspartame

Nonproprietary Names

BP: Aspartame
PhEur: Aspartamum
USPNF: Aspartame

Synonyms: 3-Amino-N-(aì-carboxyphenethyl) succinamic acid N-methyl ester; 3-amin N(aìmethoxycarbonylphenethyl) succinamic acid; APM; aspartyl phenylamine methyl ester.

Chemical Name: N-aò-L-Aspartyl-L-phenylalanine 1-methyl ester

Empirical Formula: C14H18N2O5

Molecular Weight: 294.31

Functional Category: Sweetening agent

Description: Aspartame occurs as an off white, almost odorless crystalline powder with an intensely sweet taste.

Applications in Pharmaceutical Formulation or Technology: Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets, powder mixes, and vitamin preparations. It enhances flavor systems and can be used to mask some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose. Unlike some other intense sweeteners, aspartame is metabolized in the body.

Stability and Storage Conditions: Aspartame is stable in dry conditions. In the presence of moisture, hydrolysis occurs to form the degradation products.

Mannitol (Singh *et al*., 2009)

Synonyms : Cordyceptic acid, manita, manna sugar, Pearlitol.

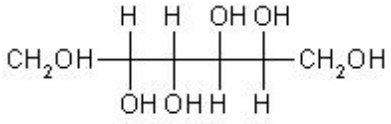
Chemical name: 1-Ethenyl-2-pyrrolidinone homopolymer.

Description: White, odourless powder or free flowing granules. It has a sweet taste.

Functional category: Tablet and capsule diluent, sweetening agent, tonicity agent, vehicle (bulking agent) for lyophilized preparations.

Solubility : Freely soluble in water practically insoluble in ether.

Structural formula



Storage conditions: Bulk materials should be stored in a well closed container in a cool and dry place.

Safety: When consumed orally in large amount laxative effect may occur.

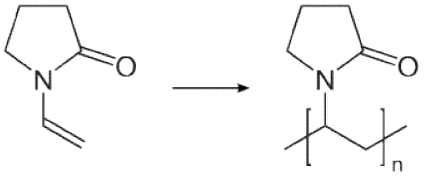
Applications

- As a diluent in tablets (10-90% w/w).
- It is not hygroscopic and can be used in moisture sensitive active ingredients.
- In the manufacture of chewable tablet formulations because of negative heat of solution.

Poly vinyl pyrollidone (Swamy *et al*., 2008)

Synonyms: Povidone, Copovidone PVPP, Crospovidone.

Structural formula:



Chemical Name: 1- -ethenylpyrrolidin-2-one

Molecular formula: $(C_6H_9NO)_n$

Description: White to light yellow, hygroscopic, amorphous powder

Solubility: Soluble in water and other polar solvents

Functional category: Binder

Applications: Used as dry binder along with ethanol. Suspension stabilizer, film coater, bioavailability enhancer.

METHODOLOGY

Materials used with their source:

Table: Materials used in study

Equipments

Table: Equipment Used In Study

S. No.	Equipment	Model	Make/Model
1	Tablet compression machine	82505	Cadmach
2	Hardness Tester	OSSCO	Monsanto Hardness Tester
3	Friability Test Apparatus	INCO	Instrument & chemicals. Pvt. Ltd, India
4	Tablet Dissolution Test Apparatus	TDT 08L	Electrolab USP
5	UV Visible Spectrophotometer	SL 164	ELICO, Double beam UV, Visible spectrophotometer
6	Balance	AUX 220	Shimadzu Digital Balance
7	pH meter	LT 120	ELICO

Preparation of calibration curve for amiodorone

Standard curve in ph 6.8 phosphate buffer

1. Stock Sample Preparation

Accurately weighed 100 mg of drug (Amiodorone) was first dissolved in100 ml of pH 6.8 phosphate buffer in 100 ml of volumetric flask to make a concentration of 1000 µg/ml (primary stock solution). 5 ml of primary stock solution was pipetted out into 50 ml of volumetric flask and volume was adjusted with pH 6.8 phosphate buffer to make a concentration of 100µg/ml (secondary stock solution).

2. Sample Preparation

From the secondary stock solution pippetout 0.5, 1.0, 1.5,2.0,2.5 and 3.0in to 10ml of volumetric flask and volume made up to with 6.8pH Phosphate buffer to give various concentrations such as5,10,15,20,25 and 30µg/ml were prepared for calibration curve. Standard curve was plotted by taking absorbance of secondary stock solutions in UV double beam spectrophotometer at 254nm.

Drug-excipient compatibility studies

Fourier Transform Infrared (FTIR) Spectroscopy

The Fourier transform infrared (FTIR) spectra of samples were obtained using FTIR spectrophotometer (Perkin Elmer). Pure drug, individual polymers and optimized formulations were subjected to FTIR study. About 2–3 mg of sample was mixed with dried potassium bromide of equal weight and compressed to form a KBr disk. The samples were scanned from 400 to 4000 cm^{-1}.

Preparation of Oro Dispersible Tablets by Physical Mixture

Direct Compression

Amiodorone (100mg) and all the ingredients were accurately weighed and passed through sieve #40. Amiodorone was well mixed with weighed quantity of ingredients i.e., Sodium starch glycolate, Cros-carmellose sodium, Cros-povidone, Mannitol, Aspartame, citric acid, and Microcrystalline cellulose in geometric proportions. Mixed homogeneously in a polybag for about 5 -10min. Then the lubricated blend was subjected to compression on a sixteen station rotary tablet punching machine using 8mm circular standard flat faced punches.

Table: Formulation of Amiodorone tablets Prepared by Direct Compression

Composition (%)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Amiodorone (mg)	200	200	200	200	200	200	200	200	200
Sodium starch glycolate	5		--	7.5	--	--	10	--	--
Crosspovidone	--	5	--	--	7.5	--	--	10	--
Cros-carmellose sodium	--	--	5	--	--	7.5	--	--	10
PVP	5	5	5	5	5	5	5	5	5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mannitol	25	25	25	25	25	25	25	25	25
Aspartame	0.5	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
DCP	qs	Qs	Qs	qs	qs	Qs	qs	qs	qs
Total weight	350	350	350	350	350	350	350	350	350

Evaluation of tablets

a) Weight Variation Test

From each batch twenty tablets were selected at a random and average weight was determined (*Venkateswarlu et al.,).* Then individual tablets were weighed and the individual weight was compared with an average weight, the variation in the weight was expressed in terms of % deviation.

b) Hardness and Friability Test

For each formulation the hardness was determined by using Monsanto hardness tester and Friability of the tablets was

checked by using Roche Friabilator. This device subjects a tablets to the combined effect of abrasion and shock by utilizing plastic chamber which revolves at 25 rpm dropping the tablets at a distance of 6 inches with an each revolution (*Mona nagar et al.,)*. Preweighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions.

c) Drug Content Uniformity Study

Five tablets were weighed individually and powdered. The powder equivalent to 2 mg of meloxicam was weighed and extracted in phosphate buffer pH 6.8 (100 ml) and the concentration of drug was determined by measuring absorbance at 363nm by spectrophotometer.

d) *In-vitro* Drug Release Study

Dissolution rate was studied by using USP type-II apparatus at 50 rpm (USP XXIII Dissolution Test Apparatus) using 900 ml of phosphate buffer PH 6.8 as dissolution medium. Temperature of the dissolution medium was maintained at 37±0.5ºC; aliquot of dissolution medium was withdrawn at every 5 minute interval and filtered. The absorbance of filtered solution was checked by UV spectrophotometric method at 254 nm and concentration of the drug was determined from standard calibration curve.

***In-vitro* drug release studies details**

- Apparatus used : USP XXIII dissolution test apparatus
- Dissolution medium : 6.8 pH phosphate buffer solution
- Dissolution medium volume : 500 ml
- Temperature : 37±0.5ºC
- Speed of basket paddle : 50 rpm
- Sampling intervals : 5 min
- Sample withdrawn : 5 ml
- Absorbance measured : 254 nm

RESULTS AND DISCUSSION

Standard Calibration Curve of AmiodaroneHCl

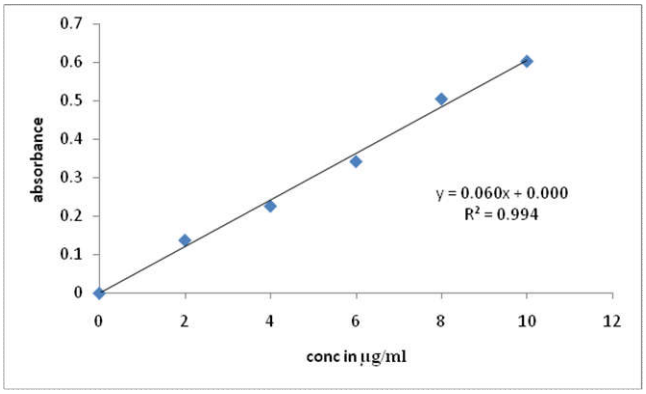


Fig: Standard calibration curve of Amiodarone HCl

a. Bulk density and tapped density

Bulk density and tapped density of powder blend was evaluated (*Dali Shukla, Subhashis Chakraborty et al.,)*. The results were shown in the Table N0.08.

b. Angle of Repose

The angle of repose for the entire formulations blend was evaluated. The results were shown in the Table No.08 range from 40-44.

c. Compressibility Index

Compressibility index for the entire formulations blend was evaluated. The results were shown in the Table No.08,range from 21-23.

d. Hausner`s Ratio

The Hausner`s ratio for the entire formulations blend was evaluated. The results were shown in the Table No. 08, range from 1.55-1.64. All these are within the limit. From the investigation, it can be demonstrate that it is possible to develop Amiodarone by a simple direct compression withsuperdisintegrants. The supplied drug passed the various

Table: Standard Calibration Curve of Amiodarone HCl

S.No.	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.138
3	4	0.227
4	6	0.343
5	8	0.506
6	10	0.604

Table: Preformulation parameters of Amiodarone HCl tablets Prepared by Direct Compression method

S.No.	Formulations	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Compressibility index (%)	Angle of repose (^{0})	Haunser'sratio
1	F1	0.42	0.54	22	28	1.58
2	F2	0.43	0.56	22	27	1.56
3	F3	0.45	0.58	23	28	1.60
4	F4	0.44	0.54	22	26	1.64
5	F5	0.48	0.59	21	25	1.62
6	F6	0.42	0.54	23	28	1.56
7	F7	0.5	0.60	17.5	29	1.21
8	F8	0.4	0.47	16	28	1.19
9	F9	0.5	0.60	17.5	28	1.21

tests of identification and analysis. The pure drug Amiodarone and the solid admixture of drug and various excipients used in the preparation of fast dispersible tablet formulations were characterized by FT-IR spectroscopy to know the compatability. The FT-IR study did not show any possibility of interaction between Amiodarone and superdisintegrants used in the fast dispersible tablets. Orodispersible tablets of Amiodarone were prepared by direct compression method employing combination of two super-disintegrants at a time. Sodium starch glycolate (SSG), croscarmellose sodium (CCS) and crospovidone (CP) were used as super-disintegrants while microcrystalline cellulose (MCC) and directly compressible mannitol (Pearlitol SD200) were used as diluent and sweetening agent respectively.

Table: Post formulation parameters of Amiodarone tablets

Formula code	Hardness (Kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)	*In-vitro* Disintegration Time(sec)
F1	4.5± 0.5	348 ±2	<0.22	98.99	29
F2	4.9± 0.5	349 ± 2	<0.24	99.01	26
F3	4.1± 0.5	350 ± 3	<0.22	96.56	24
F4	4.3± 0.5	347± 4.	<0.19	98.65	20
F5	4.8± 0.5	349 ± 2	<0.17	97.6	15
F6	4.5± 0.5	351 ± 3	<0.16	96.2	18
F7	4.6± 0.5	354 ± 3	<0.24	98.09	08
F8	4.8± 0.5	347± 4.	<0.22	98.5	13
F9	4.7± 0.5	349 ± 2	<0.19	97.6	13

Evaluation of tablets

Hardness

Tablet mean thickness was almost uniform in all the formulations. The prepared tablets in all the formulations possessed good mechanical strength with sufficient hardness in the range of 4.1 ± 0.5 to 4.9 ± 0.5 kg/sq cm. Shown in table no.09.

Friability

Friability values below 1% were an indication of good mechanical resistance of the tablets.

Weight variation

All the tablets from each formulation passed weight variation test, as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weight variation in all the six formulations was found to be 197.98 to 201.15 mg, which was in pharmacopoeial limits of ±7.5% of the average weight. Shown in table no.09

Drug content

The percentage drug content of all the tablets was found to be between 96.20 to 99.01 % of Amiodarone which was within the acceptable limits. Shown in table no.09.

Invitro disintegration

The formulations containing single super disintegrant showed *invitro* disintegration time 08-29sec. Hence it was decided to use a combination of two super-disintegrants so that orodispersible tablets with *invitro* disintegration time of less than 15 s may be developed. The wetting time, of the tablets were also considerably reduced in tablets containing Sod. starchglycolate which may be attributed due to the wicking type of disintegrants(Sod. starch glycolate,karaya gum) formed thus facilitating thedisintegrants to bring about faster disintegration. The *invitro* dissolution profile indicated faster and maximum drug release from formulation F7. The disintegration time of guargum and karaya gum tablets are comparatively lower than the sodium starch glycolatealone. The faster disintegration of Sodium Starch glycolate tablets may be attributed to its rapid capillary activity and pronounced hydration with little tendency to gel formation.

Table: Cumulative Percent Drug Release of tablets

Sampling time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	56	56	39	45	54	59	73	26	30
10	63	59	47	54	58	65	84	41	38
15	67	60	61	59	65	72	89	49	50
20	69	62	61	64	69	72	99	60	70
30	71	64	68	69	72	78	--	72	85
45	75	65	74	74	76	81	--	84	100.1
60	76	67	79	96	80	86	--	98	

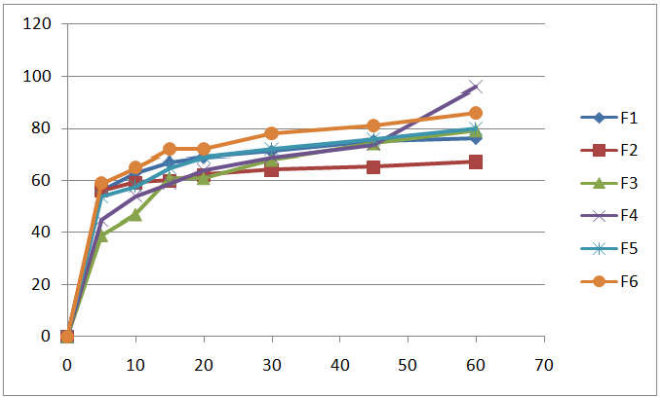


Fig: Plot of drug release versus time for F1 to F6

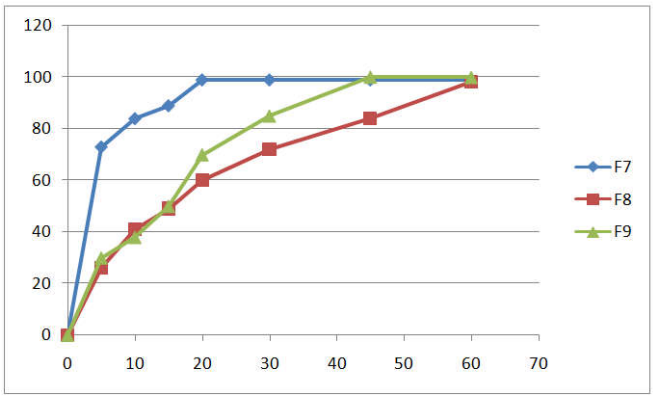


Fig: Plot of drug release versus time for F7 to F9

Conclusion

The oral disintegrating tablets of Amiodarone with sufficient mechanical strength, acceptable taste and smaller disintegration time were achieved employing suitable superdisintegrants and other excipients at optimum concentration. FTIR studies revealed that there was no shift in peaks, indicating there is no interaction between Amiodarone and other ingredients used. The conventional method of dissolution could be extended to in-vitro evaluation of MDT

The dissolution conditions for the reference listed drugs available in USP can be utilized for preliminary in-vitro studies to mimic better in-vivo conditions. At present, the disintegration time of MDTs is measured using the disintegration test for conventional tablets that is described in the Pharmacopoeias. EP has set the limit of 3 minutes for disintegration time of MDTs using conventional disintegration apparatus. However, no special apparatus is mentioned in the pharmacopoeias for disintegration test of MDTs and the conventional method available seems to be inappropriate for MDTs. This is because of the extreme operating conditions in the disintegration apparatus which fails to provide a significant discrimination among the rapidly disintegrating tablets. The formulation's organoleptic properties like taste, mouth-feel and appearance are of considerable importance in differentiating products in the market and can ultimately determine the success of a product. Hence, the above results lead us to believe that concentrations of disintegrants have an important role to play, and optimal concentrations in fast dissolving tablets give rise to rapid disintegration times, good crushing strength values, and sufficiently low friability percentages, in order to successfully withstand the mechanical stress, during packing, transportation and handling. Natural superdisintegrants exhibits faster drug dissolution and improved bioavailability, thereby helping in effective therapy and improved patient compliance.

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