THINK INDIA JOURNAL

ISSN: 0971-1260
Vol-22-Issue-35 -December -2019

Formulation and Evaluation of Freeze Dried Tablet of Atenolol

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Introduction

The demand for more patient-friendly and complaint dosage forms has increased for past one decade. As an outcome, the demand for developing new technologies has been growing annually. As the development cost of a new drug molecule is very high, the pharmaceutical companies are finding out new drug dosage forms for existing drugs with developed safety and efficacy together with reduced dosing and the production of more cost effective dosage forms.

For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of administration, owing to its several advantages and high patient compliance compared to many other routes.

The currently available drug delivery system mains constitute tablets and hard gelatin capsules.

However, many patient groups such as the elderly, children, and patients who are mentally retarded, uncooperative, nauseated, or on reduced liquid-intake/diets have difficulties swallowing these dosage forms. Those who are traveling or have little access to water are similarly affected.

To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as Orally Disintegrating Tablets (ODTs) which disintegrate rapidly in saliva, usually in a matter of seconds, without the need to take it water. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms.

Although chewable tablets have been on the market for some time, they are not the same as the new ODTs. Patients for whom chewing is difficult or painful can use these new tablets easily. ODTs can be used easily in children who have lost their primary teeth but do not have full use of their permanent teeth. Recent market studies indicate that more than half of the patient population prefers ODTs to other dosage forms and most consumers would ask their doctors for ODTs (70%), purchase ODTs (70%), or prefer ODTs to regular tablets or liquids (>80%).

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ISSN: 0971-1260
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The US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, in the 'Orange Book', an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". The significance of these dosage forms is highlighted by the adoption of the term, "Orodispersible Tablet", by the European Pharmacopoeia which describes it as a tablet that can be placed in oral cavity where it disperses rapidly before swallowing.

ODT products have been developed for numerous indications ranging from migraines (for which rapid onset of action is important) to mental illness (for which patient compliance is important for treating chronic indications such as depression and schizophrenia).

1.1 Descriptions of Orally Disintegrating Dosage Forms

ODTs are distinguished from conventional sublingual tablets, buccal tablets, and lozenges, which require more than a minute to dissolve in oral cavity. In the literature, ODTs also are called orodisperse, mouth-dissolving, quick-dissolve, fast-melt, and freeze-dried wafers.

A freeze-dried wafer is a quick-dissolving, thin matrix that contains a medicinal agent that does not need water for swallowing. This fragile dosage form requires unit-dose packaging to ensure physical stability. The wafer disintegrates instantaneously in the oral cavity and releases drug, which dissolves or disperses in the saliva. The saliva is swallowed and the drug is absorbed across the gastrointestinal tract (GIT).

An orally disintegrating tablet (ODT) 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.

A quick-dissolving tablet (also known as a fast-dissolving, fast-dissolving multiparticulate, rapid-dissolving, mouth-dissolving, fastmelting, or orodispersing tablets) is an oral tablet that does not require water for swallowing. The tablet dissolves within 60 seconds when placed in the mouth. The active ingredients are absorbed through mucous membranes in the mouth and GIT and enter the blood stream. A fraction of pregastric drug absorption may bypass the digestive system and metabolism by the stomach acids and enzymes. In general, the tablets are physically robust and can be packaged in multidose containers.

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ISSN: 0971-1260
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1.2 Ideal properties of ODTs

The performance of ODTs depends on the technology used during their manufacture. The necessary property of such tablets is the ability to disintegrate rapidly and disperse or dissolve in saliva, thereby obviating the need for water. Various technologies have been developed that enable ODT to perform this unique function. An ideal ODT should meet the following criteria:

• does not require water for oral administration yet disintegrates and dissolves in oral cavity within a few seconds

• has sufficient strength to withstand the rigors of the manufacturing process and post-manufacturing handling

• allow high drug loading

• has a pleasant mouth feel

• is insensitive to environmental conditions such as humidity and temperature

• is adaptable and amenable to existing processing and packaging machineries

• is cost-effective.

1.3 The Need for Development of ODTS

The need for non-invasive delivery systems persists due to patients' poor acceptance of, and compliance with, existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management.

1.3.1 Patient factors

Orally disintegrating dosage forms are particularly suitable for patients, who for one reason or the other, find it inconvenient to swallow traditional tablets and capsules with an 8-oz glass of water. These include the following:

• Pediatric and geriatric patients who have difficulty in swallowing or chewing solid dosage forms

• Patients who are unwilling to take solid preparation due to fear of choking

• Very elderly patients who may not be able to swallow a daily dose of antidepressant.

• An eight-year old with allergies who desires a more convenient dosage form than antihistamine syrup

• A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2- blocker

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ISSN: 0971-1260
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• A schizophrenic patient in an institutional setting 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

1.3.2 Effectiveness factor

Increased bioavailability and faster onset of action are a major claim of these formulations. Dispersion in saliva in oral cavity causes pregastric absorption from some formulations in those cases where drug dissolves quickly. Buccal, pharyngeal and gastric regions are all areas of absorption for many drugs. Any pregastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo a great deal of hepatic metabolism. 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 pregastric segments of GIT.

1.3.3 Manufacturing and marketing factors

Developing new drug delivery technologies and utilizing them in product development is critical for pharmaceutical industries to survive, regardless of their size. 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 ODT, 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 LipolaM (simvastatin ODT), 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 company image when they offer a unique easier-to-take form that satisfies the need of an underserved patient population.

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ISSN: 0971-1260
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1.4 Challenges in Formulating ODTS

1.4.1 Palatability

As most drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in patient's oral cavity, thus releasingthe active ingredients which come in contactwith the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance.

1.4.2 Mechanical strength

In order to allow ODTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may add to the cost. Only few technologies can produce tablets that are sufficiently hard and durable to allow them to be packaged in multidose bottles, such as Wowtab® by Yamanouchi-Shaklee, and Durasolv® by CIMA labs.

1.4.3 Hygroscopicity

Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging.

1.4.4 Amount of drug

The application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers.

1.4.5 Aqueous solubility

Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming

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ISSN: 0971-1260
Vol-22-Issue-35 -December -2019

excipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite.

Size of tablet

The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.

Selection of ODT Drug Candidates

Several factors must be considered when selecting drug candidates for delivery as ODT dosage forms. In general, an ODT is formulated as a bioequivalent line extension of an existing oral dosage form. Under this circumstance, it is assumed that the absorption of a drug molecule from the ODT occurs in the postgastric GIT segments, similar to the conventional oral dosage form.

But this scenario may not always be the case. An ODT may have varying degrees of pregastric absorption and thus, the pharmacokinetic profiles will vary. Therefore, the ODT will not be bioequivalent to the conventional oral dosage form. For example, ODT formulations of selegiline, apomorphine, and buspirone have significantly different pharmacokinetic profiles compared with the same dose administered in a conventional dosage form.

It is possible that these differences may, in part, be attributed to the drug molecule, formulation, or a combination of both. If significantly higher plasma levels have been observed, pregastric absorption leading to the avoidance of first-pass metabolism may play an important role. This situation may have implications for drug safety and efficacy, which may need to be addressed and assessed in a marketing application for an ODT33. For example, safety profiles may be improved for drugs that produce a significant amount 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 segments of the pregastric GIT. Drugs having ability to diffuse and partition into the epithelium of the upper GIT (log P> 1, or preferable > 2); and those able to permeate oral mucosal tissue are considered ideal for

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ISSN: 0971-1260
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ODT formulations. Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs. Similarly, patients with Sjögren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations. Drugs with a short half-life and frequent dosing, drugs which are very bitter or otherwise unacceptable taste because taste masking cannot be achieved or those which require controlled or sustained release are unsuitable candidates of rapidly dissolving oral dosage forms.

Researchers have formulated ODT for various categories of drugs used for therapy in whichrapid peak plasma concentration is required to achieve the desired pharmacological response. These include neuroleptics, cardiovascular agents, analgesics, antiallergic, anti-epileptics, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction.

1.6 Approaches to ODT Development

The fast disintegrating property of the tablet is attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration. Hence, the basic approaches to develop rapidly dissolving oral dosage forms include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water soluble excipients in the formulation. As is often the case, a technology that is originally developed to address a particular administration need can quickly become adopted as part of a pharmaceutical company's product life cycle management strategy, which is precisely what has happened with ODT technologies.

Broadening the scope of ODT technologies Industry observers point to broadening uses of ODT technology. These include the incorporation of macromolecules using ODT into vaccines. The success for other peptide and protein products will depend on bioavailability requirements and the application of methods to overcome oral absorption barriers. Other areas include: the incorporation of encapsulated APIs to achieve modified-release profiles within the convenience of an ODT; and the further development of super disintegrates for incorporation into conventional, compressed tablets, potentially widening the opportunity for ODT development to non-specialist companies.

Another emerging area is the wider application of 'oral thin-strip technologies'. The use of thin-film strips is of growing interest in the pharmaceutical sector following the success of Listerine PocketPaks® in the United States. Thin-film strip technology uses a range of water-

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ISSN: 0971-1260
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soluble polymers and is reported to be able to incorporate water soluble, insoluble, or taste-masked ingredients. The film is manufactured as a continuous sheet and then cut into individual doses prior to packing. The major limitations to this technology are the relatively low doses that can be accommodated (approximately 30 mg) and its moisture sensitivity thus requiring specific unit-dose packaging to protect the product and ensure shelf life. Thin-film technology has primarily been used in over the- counter (OTC) products.

Review of literature

Panda et al (2018), prepared vilazodone sublingual tablets by using lyophilization technique. It is a BCS Class – II drug, offer challenges in developing a drug product with adequate bioavailability. The aim of present investigation was to formulate and evaluate vilazodone sublingual tablets using poloxamer 407 as a carrier by lyophilized solid dispersion technique. The lyophilized solid dispersion of vilazodone prepared by poloxamer 407 (1:5) showed more than 85% drug release within 5 min, so it was used for the development of sublingual tablets by direct compression technique. The physicochemical, solid-state properties, dissolution behaviour of lyophilized solid dispersion as well as sublingual tablets were evaluated. Finally, the bioavailability studies of the prepared tablets were performed by sublingual administration to rabbits. The sublingual tablets showed a higher in vitrodis solution rate and bioavailability compared with the commercial tablets. It is evident from the results herein that the developed sublingual tablets provide a promising drug delivery system in drug development, owing to their excellent performance of a rapid onset of action and improved bioavailability.

Hazzaa et al (2017), Optimized Zaltoprofen Lyophilized Tablets by Zydis Technique. The lyophilized disintegrating tablets (LDTs) were prepared using Zydis technique by lyophilization an aqueous dispersion of Zaltoprofen with a matrix forming agent, gelatin, and a collapse protectant, glycine. In addition to many excipients like PVPK30 was used to improve the in vitro, in vivo disintegration time and dissolution rate, mannitol as bulk forming agent. Fourteen formulations were prepared to inspect the variables that affect the disintegration time and dissolution rate. All the formulations were evaluated for their physical appearance, mechanical strength, X-ray diffraction, FTIR, DT, and in vitro drug release. The prepared tablets were optimized and formula was subjected to different measured parameters such as disintegration time, Drug content, and in-vitro drug release. Results obtained from

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ISSN: 0971-1260
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dissolution studies and DT showed that lyophilized disintegrating tablets (LDTs) (F8,F10,F12,F13 was 45,37,21 and 17 Sec.) respectively ,while(F14) displayed considerably faster in vitro dissolution rate of (Zaltoprofen) 3 min. and DT 9 sec. The (lyophilized disintegrating tablets) were also evaluated showing the transformation into amorphous state and absence of interaction of Zaltoprofen with the components of the tablets. From visual inspection ,physical strength ,DT and release behavior obtained ,one can conclude that the formulas(F14) which contains Zaltoprofen 3.2% ,gelatin3%, mannitol 3%, glycine 1.5%, PVP K30 1.5% was the most suitable one.

Salama et al (2017),designed lyophilized dry emulsion tablets for enhancing the antihyperlipidemic activity of atorvastatin calcium. Tablets were fabricated by freeze-drying o/w emulsions of ATV. The Emulsions were prepared using a matrix former solution (alginate or gelatin, 2 or 4%) containing a sugar alcohol (mannitol) and a collapse protectant (glycine) as the water phase and Labrafac® as the oil phase in the presence of surfactant (synperonic® PE/P 84 or synperonic® F108) under proper homogenization. The influence of formulation parameters on friability of the prepared tablets, disintegration time and in-vitro dissolution of the drug from these tablets were investigated. Results showed the significant influence of the matrix former and emulsifier type on the disintegration time. In-vitro dissolution study revealed the enhanced dissolution rate of ATV from the lyophilized dry emulsion tablets (LDET) compared to the plain drug. DSC and XRD studies of the optimized ATV-loaded LDET proved the presence of the drug in the amorphous form. SEM images showed the intact, porous and non-collapsible structure of the prepared LDET with complete loss of ATV crystallinity. Administration of ATV-loaded LDET to high fat diet-induced hyperlipidemic rats demonstrated a significant decrease ($p<0.05$) in the serum and tissue levels of the tested parameters compared to the market product used. The obtained results suggest a promising, easy-to-manufacture and effective dosage form for the treatment of hyperlipidemia.

Dave et al (2016) prepared novel fast dissolving tablet of chlorpheniramine maleate by using lyophilization techniques. Lyophilization(freeze-drying) is a process in which water is sublimated from the product after freezing at a specific temperature and pressure. Lyophilization technique is used in order to improve the dissolution of the given substance and improve the oral bioavailability of the drugs with poor solubility and high permeability.

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In this work, chlorpheniramine maleate FDTs was formulated by lyophilization method. The prepared tablets were subjected to various evaluation such as hardness (2.4–2.9 kg/cm2), friability (0.68–0.79%),
disintegration time (10–19 s), drug content (95.32–99.09%), water absorption ratio (31–53%), wetting time (64–106 s) and in-vitro drug release shown in 5 min (96.04–99.92%). FTIR studies showed that there is no interaction between drug and polymer. Stability studies showed that there is no change in drug content within three and six months. Results revealed that fast dissolving tablets of chlorpheniramine maleate prepared by lyophilization method result in rapid dissolution.

Liew et al (2015) prepared a user friendly and convenient dosage form Orally disintegrating tablet (ODT) containing daposetine. The study aimed to investigate the effect of polymers and wheat starch on the tablet properties of lyophilized ODT, with dapoxetine as model drug. Three polymers (hydroxypropylmethyl cellulose, carbopol 934P and Eudragit EPO) and wheat starch were used as matrix forming materials in preparation of lyophilized ODT. The polymeric dispersion was casted into a mould and kept in a freezer at -20 C for 4 h before freeze dried for 12 h. It was found that increasing in HPMC and Carbopol 934P concentrations produced tablets with higher hardness and longer disintegration time. In contrast, Eudragit EPO was unable to form tablet with sufficient hardness at various concentrations. Moreover, HPMC seems to have a stronger effect on tablet hardness compared to Carbopol 934P at the same concentration level. ODT of less friable was obtained. Wheat starch acted as binder which strengthen the hardness of ODTs and prolonged the disintegration time. ODT comprising of HPMC and wheat starch at ratio of 2:1 was found to be optimum based upon the tablet properties. The optimum formulation was palatable and 80 % of the drug was released within 30 min in the dissolution study.

Karsono et al (2014), prepared Ibuprofen Orally Disintegrating Tablets (ODTs) by Lyophilization Method using Gelatin and Mannitol. Ibuprofen ODTs were formulated by using water soluble matrix consisting gelatin 5% and mannitol in the ratio 0:200; 50:150; 100:100; 150:50; 200:0. The resulting tablets were evaluated using parameters such as: hardness, friability, disintegration time in vitro, modified disintegration time, disintegration time in the oral cavity, wetting time, water absorption ratio, drug content determination, weight uniformity, and dissolution. The results showed that ibuprofen Orally Disintegrating

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Tablets fulfilled the requirements for all parameters except for F5 formula that did not produce physical shape intact tablet. ODTs used higher amount of gelatin 5% showed faster disintegration time [19 s (F1); 29.2 s (F2); 36 s (F3) and 57.5 s (F4)]. In contrast, the higher amount of mannitol used in ODTs formula, tablet hardness were also higher. In vitro drug release of all formulation ODTs showed fast drug release in the first minute where the F1 97.77%; F2 89.66%, 87.80% F3; F4 72.97%, much different with pure ibuprofen only release 27.15%. From ANOVA test using SPSS program 15.0 ($p < 0.05$) showed significant differences dissolution profiles between all ODTs formula with pure ibuprofen.

Experimental

Table 1: Active Pharmaceutical Ingredients (API)

Sr. No.	Active Pharmaceutical Ingredients (API)	Source/Manufacturer
1.	Atenolol	HelioxPharma

Table 4: Chemicals used during the Experimental work

Sr. No.	Chemical/Material	Source/Manufacturer
1	Eudragit EPO	Evonik
2	HPMC E5	Colorcon, Asia
3	Potassium dihydrogen Orthophosphate	Fischer Scientific, Mumbai
4	Sodium dihydrogen orthophosphate	Fischer Scientific, Mumbai
5	Methanol	Fischer Scientific, Mumbai
6	HCl	Qualichem, Mumbai
7	n-octanol	Qualichem. Ltd, Mumbai
8	Mannitol	Quallichem, Mumbai

Table 2: Equipment used during the experimental work

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Sr. No.	Equipment	Manufacturer
1	Mechanical Stirrer	Raj Analytical Services, Mohali, India
2	Electronic weighing balance	Shimadzu, Japan
3	FTIR	Bruker Alpha, Berlin, Germany
4	Eppendorf tubes	Tarsons Products Pvt. Ltd., Kolkata, India
5	Hot air oven	Narang Scientific Works, New Delhi, India
6	Magnetic stirrer	Remi Scientific Instruments, Mumbai
7	Freeze dryer	Virtis, USA
8	Microcentrifuge	Remi Scientific Instruments, Mumbai
9	Vacuum pump	Suguna single phase, Chennai, India
10	Micropipette	Accupipet, Mumbai, India
11	pH meter	Labindia Ltd., Mumbai, India
12	UV spectrophotometer	Shimadzu, Japan
13	Vials	Tarsons Products Pvt. Ltd., Kolkata, India
14	Vortex-type mixer	Remi Scientific Instruments, Mumbai

Preformulation studies

Preformulation studies are the leading phase in the development of dosage forms that can be well-defined as "investigation of physical and chemical properties of a drug substance alone and when it combines with excipients". These physicochemical studies should focus on properties of a new compound that could affect the drug development and performance of an effective dosage form. A thorough understanding of physicochemical properties of a drug is

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ISSN: 0971-1260
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necessary that may ultimately provide a rationale formulation design or support the need for molecular modification.

The goals of preformulation are:

- To establish the necessary physiochemical parameters of new drug substances.
- To determine kinetic rate profile.
- To establish physical characteristics.
- To establish compatibility with common excipient.

  Therefore, preformulation studies are compulsory to establish the identity and physicochemical parameter of selected drug combination Atenolol was subjected for following investigations:
- Organoleptic Properties
- UV- VIS spectroscopy
- FTIR spectroscopy
- Melting point
- Partition coefficient
- Solubility

2.1.1. Organoleptic Properties

The organoleptic studies like general appearance like nature, color, odor etc. were performed by visual observations.

Color: Small amount of drug was taken in butter paper and viewed in well illuminated place.

Odor: Very less quantity of drug was smelled to get the odor.

UV-VIS spectra

UV spectrophotometery is mainly used for qualitative and quantitative analysis of drugs and serves as a useful auxiliary tool for structural elucidation. It deals with the measurement of energy absorbed when electrons are excited from lower energy state to higher energy state. 10 µg/ml solution of Atenolol was prepared separately and scanned in the range of 200-400 nm using UV-VIS spectrophotometer.

- **Preparation of standard curve of Atenolol in methanol(DMF)**

10 mg of Atenolol was weighed accurately and transferred into 100 ml volumetric flask then the volume was made up with DMF to get 100 µg/ml stock solution of Atenolol. The solution

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ISSN: 0971-1260
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was sonicated for 5 min. This solution was further diluted with DMF to get 1-10 µg/ml of Atenolol by serial dilution method and samples are analyzed by UV spectrophotometer using DMF as blank [112].

Melting point of drug

The melting point of a solid is the temperature at which the solid exists in equilibrium with its liquid state under an external pressure of one atmosphere. Capillary tube method was used for the determination of the melting point of Atenolol. USP had described specifications for capillaries for melting point determinations i.e. 10 cm length, 0.8-1.2 mm internal diameter and 0.2-0.3 mm wall thickness, sufficient amount of the dry powder should be packed down to form a 2.5-3.5 mm high column in the bottom of the tube. Atenolol was placed in the vacuum desiccator at room temperature and was dried for about 24 hrs. Then the dried drugs were tightly filled in the capillary tubes up to 3 mm by tapping the closed end of capillary on a solid surface. Finally, melting point was determined using melting point apparatus [113].

Partition coefficient of drug

The partition coefficient of a chemical compound provides a thermodynamic measure of its hydrophilic/lipophilic balance. Hence, it has been become one of the most frequently described physical properties of drug. Partition coefficient is the ratio of concentrations of a drug substance in the mixture of two immiscible solvents at equilibrium. The partition coefficient is commonly determined by using an oil phase of n-octanol and water. Drugs acquiring values of Po/w enough higher than 1 are categorized as lipophilic, whereas those with partition coefficients much less than 1 are consider as hydrophilic. In the case of n-octanol and water:

$Po/w = C_{n\text{-}octanol} / C_{water}$

Procedure: Shake flask method was used for determination of partition coefficient. This is a classical and most predictable method of log P determination. Briefly, the phases of the solvent system (n-octanol and water) were mutually pre-saturated by shaking for 24 h on a mechanical shaker and then the solvents were allowed to stand long enough so that the two phases were separated and achieved a saturation state. Excess amounts of the drug (Atenolol) dissolved in 10 ml of two solvents (n-octanol: Water) together (1:1) and placed for 24 hrs. After 24 hrs, the two layers were separated and centrifuge for 15 minutes at 15,000 rpm. The absorbance was taken in UV spectrophotometer at the respective λ max after appropriate dilution.

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FTIR spectral analysis of Atenolol

FTIR spectrophotometry is used for structural and functional group analysis of drugs. The analysis was carried out using potassium bromide (KBr) pellet method. The KBr and drugs were mixed separately and carefully in a mortar while grinding with the pestle and dried completely. The powdered sample was placed just enough to cover bottom in pellet die and a pressure of 5000-7000 psi was applied to make the pellets. Then the pellets were placed in the sample holder of FTIR spectrophotometer. FTIR spectra were recorded in the 4000-400 cm-1 regions.

Drug excipients interactions

The compatibility of drug with excipients was ascertained by FTIR. FTIR was used as tool to detect any physical and chemical interaction between drug and excipient. Drug and various excipients were mixed thoroughly in ratio of 1:1. The spectra of pure drug and drug with excipients were compared to check any compatibility and physical changes**.**

Solubility studies of Atenololin solvent

The amount of a substance that dissolves in a unit volume of a liquid to form a saturated solution under specified conditions of temperature and pressure is called as the solubility of the solute. The solubility is an important physicochemical property of drug because it affects the rate of drug release, the bioavailability of the drug into the dissolution medium, and consequently, the therapeutic efficacy of the pharmaceutical product. Solubility is usually determined in various commonly used solvents and some oils if the molecule is lipophilic. The equilibrium solubility method is usually used to determine the solubility of a drug.

Procedure: For quantitative solubility study, excess amount of drug was taken in thoroughly cleaned test tubes containing 2 ml of different solvents (Methanol, Ethanol, Acetone, Chloroform, 0.1NHCl, 6.8 and 7.4 PBS, DMSO, DMF, Water) and test tubes were tightly closed. These test tubes were shaked on water bath shaker for 24 hours at room temperature. After 24hrs each sample was centrifuged 15,000 rpm and supernatant was withdrawal. After that supernatant was filtered and filtrate was suitably diluted and determined spectrophotometrically.

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Result and Discussion

3.1. Preformulation studies

The aim of preformulation studies is to investigate the physical and chemical properties of a drug substance. The selected drug Atenololwas subjected for investigation of physical characterization parameters such as:

- Organoleptic properties
- UV-visible spectra
- FT-IR spectra
- Melting point
- Solubility
- Partition coefficient

3.1.1. Organoleptic Properties

Organoleptic properties of drugAtenololfound to be as per I.P. monograph. The Organoleptic properties of Atenolol were found to the given **Table 3**.

Table 3: Organoleptic Properties of Atenolol

Sr. no.	**Properties**	**Inferences**
1	Colour	white or almost white powder
2	Odour	Odourless
3	Taste	Bitter

3.1.2. UV Spectroscopy

3.1.2.1. UV-visible spectroscopy

UV absorption maxima (λ_{max}) of Atenololin methanol was determined by using UV-visible spectrophotometer and shown in **Figure 1 and Table 4.** Drug exhibited maxima at 276 nm.

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ISSN: 0971-1260
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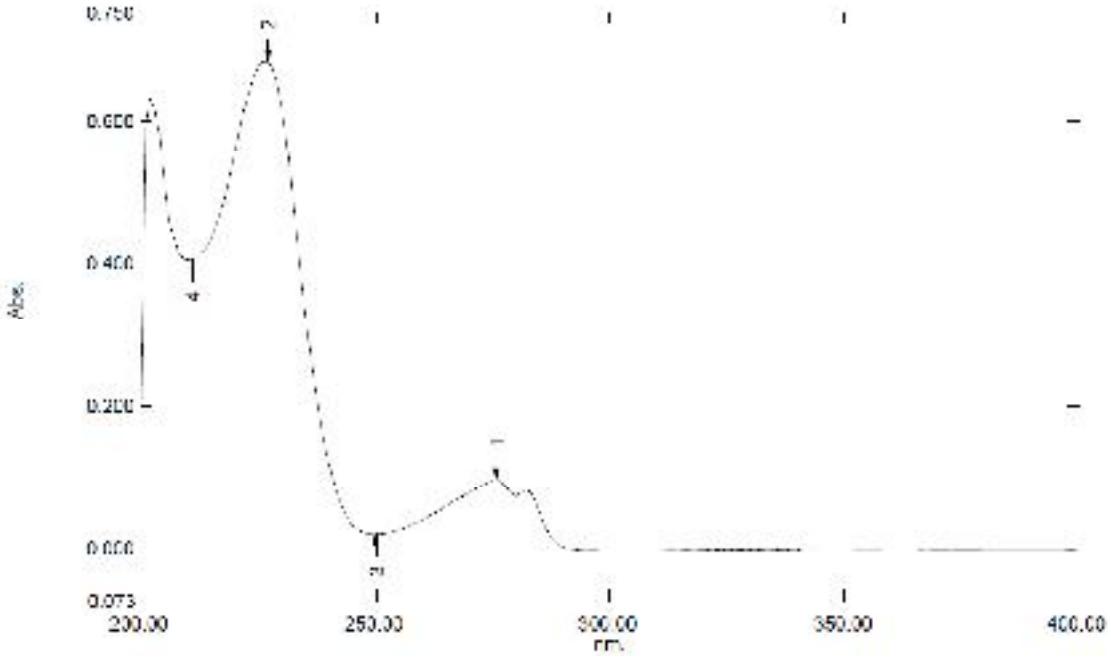


Figure 1: UV-visible spectrum of Atenololin methanol

Table 4: Absorption maxima (λ_{max}) of Atenolol

Observed absorption maxima	Reported absorption maxima
276 nm	276 nm

3.1.2.2 Preparation of standard curve of Atenololin methanol

Table 5: Calibration curve of Atenololin methanol (λ_{max}= 276 nm)

Sr.No	Concentration(µg/ml)	Absorbance
1	30	0.197±0.001
2	60	0.357333333±0.001154701
3	90	0.506666667±0.002516611
4	120	0.650666667±0.001154701
5	150	0.798±0.001
6	180	0.933666667±0.001527525

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All values are expressed as mean ± SD; n = 3

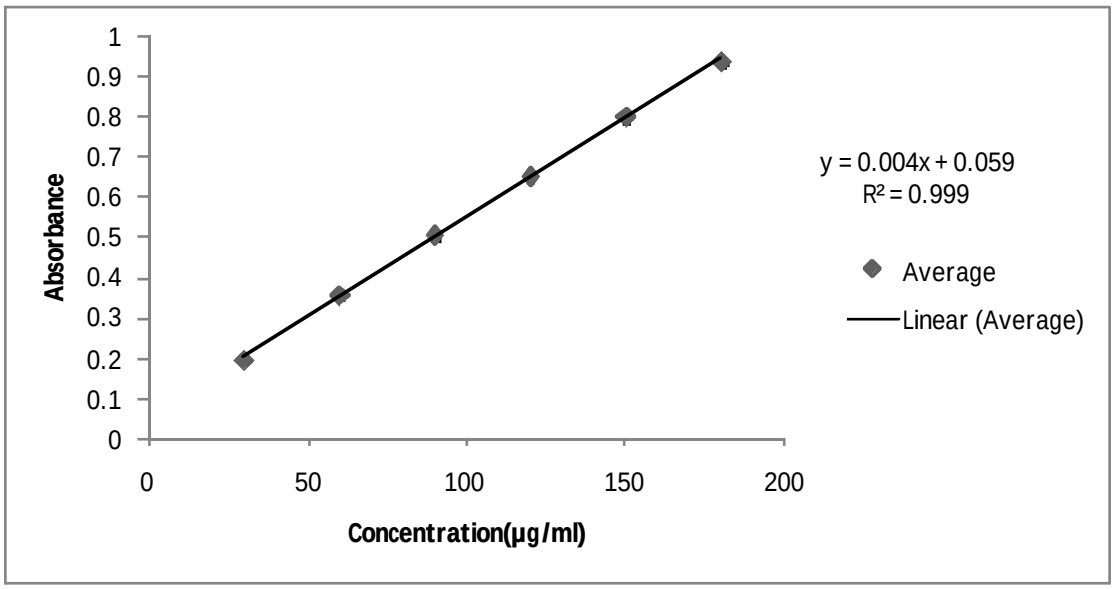


Figure 2: Graph of standard calibration curve of Atenolol in methanol

Table 6: Result of regression analysis of UV method for estimation of Atenolol

Statistical parameters	**Results**
λ max	276 nm
Regression equation ** Y=mx+C	Y=0.0049x+0.059
Slope (b)	0.049
Intercept (C)	0.059
Correlation coefficient (r^2)	0.999

Discussion: - The calibration curve for Atenolol was obtained by using the 30 to 180 µg/ml solution of Atenolol in methanol. The absorbance was measured at 276 nm. The calibration curve of Atenolol as shows in graph indicated the regression equation Y=0.0049x+0.059 and R^2 value 0.999, which shows good linearity as shown in **Table 6** and **Figure 2**.

3.1.2.2 Preparation of standard curve of Atenololin simulate saliva Ph 6.8

Table 7: Calibration curve of Atenololin simulate saliva Ph 6.8 (λ_{max} = 276 nm)

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Conc.(µg/ml)	Absorbance
30	0.134±0.001
60	0.265±0.001
90	0.405666667±0.001527525
120	0.545666667±0.001527525
150	0.685333333±0.001527525
180	0.812±0.001732051
210	0.976±0.001

All values are expressed as mean ± SD; n = 3

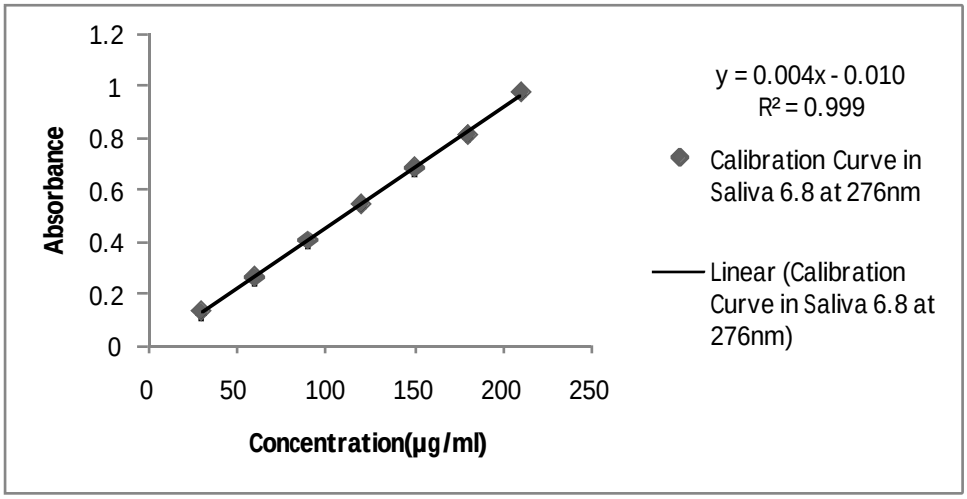


Figure 3: Graph of standard calibration curve of Atenolol in simulate saliva Ph 6.8

Table 8: Result of regression analysis of UV method for estimation of Atenolol

Statistical parameters	Results
λ max	276 nm
Regression equation ** Y=mx+C	Y=0.0046x-0.05109
Slope (b)	0.0046
Intercept (C)	0.05109
Correlation coefficient (r^2)	0.999

Discussion: - The calibration curve for Atenolol was obtained by using the 30 to 210 µg/ml solution of Atenolol in simulate saliva Ph 6.8. The absorbance was measured at 276 nm. The calibration curve of Atenolol as shows in graph indicated the regression equation Y=0.0049x+0.059 and R^2 value 0.999, which shows good linearity as shown in **Table 8** and **Figure 3**.

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ISSN: 0971-1260
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