Preparation and In-Vitro Evaluation of Candesartan Microballoons

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Abstract:
High blood pressure (HBP) is a serious condition that can lead to coronary heart disease, stroke, kidney failure and other heart problems. Microballoons of candesartan using PVP K30, HPMC, acetone, dichloromethane a copolymers were formulated to deliver candesartan microballoons via oral route. Solvent evaporation method can be successfully employed to fabricate candesartan microballoons. Micromeretic studies revealed that the mean particle size of prepared microballoons was in the size range of 512-834 microns and are suitable for microballoons for oral administration. Increase in the polymer concentration lead to increase in % drug entrapment efficiency, particle size, % swelling. The in-vitro drug release decreased with increase in the polymer and copolymer concentration. Drug release profile its under goes hepatic metabolism. and the drug release of the optimised formulation was found to be 98.55%. Stability studies are also conducted for these formulation, it considered as a stable product.

Key words: Candesartan, microballoons, sustained release products.

1. INTRODUCTION:
Microballoons (MB), a multiple unit dosage forms holding a spherical cavity surrounded by a hard polymer shell has been developed as a dosage form illustrate by excellent buoyancy in the stomach. This preparation is intend to float on surface of gastric juice, which has a specific gravity less than 1. Microballoons, loaded with drug in their outer polymer shells, develop by the emulsion solvent diffusion method by means of various polymers; dissolve in a mixture of dichloromethane and ethanol. Cavity formation in microspheres is particularly associated to evaporation of Dichloromethane. [Streubel A] The ultimate goal of any drug delivery system is effective disease/disorder management, minimum side effects and greater patience compliance in the cost effective manner. The drug therapeutic indices could be maximized while indices of adverse reactions or side effects could be minimized by regulating the drug release in body in a well-defined controlled manner. This would eliminate the hazard and uncontrolled blood plasma profiles of drug usually associated with conventional dosage forms. Microballoons can encapsulate many types of drugs including small molecules, proteins, and nucleic acids and are easily administered through a syringe needle. They are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm) Microballoons are sometimes referred to as micro particles. They are generally biocompatible, can provide high bioavailability, and are capable of sustained release for long periods of time. [Singh BN] Gastro retentive floating drug delivery system (GRFDDS) have a bulk density lower than that of gastric fluids and thus remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on gastric contents, the drug is released slowly at a desired rate from the system. Gastro retentive floating microspheres have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. Microspheres are multi particulate drug delivery systems which are prepared to obtain prolonged or controlled drug delivery to improve bioavailability, stability and to target the drug to specific site at a predetermined. [Gholap, S, Tomlinson E, Burger] Candesartan is a non-peptide angiotensin II receptor antagonist. Candesartan blocks the vasoconstriction and aldosterone secreting effects of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland, leading to a reduction in arterial blood pressure. The poor bioavailability of Candesartan (40-58%) was the criteria which caused the selection of drug, which could be increased by prolonging the gastric retention time. A previous approach for increasing the bioavailability of Valsartan by floating microspheres was reported.

Figure 1. Structure of microballoons

One of the most interesting fields of research in pharmaceutics is the development of new delivery systems for the controlled release of drugs. Gastro retentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Oral administration is...
the most convenient and preferred means of any drug delivery to the systematic circulation. [Patel DM]

**HOLLOW MICROSPHERE / MICROBALLOONS PREPARATION METHODS:**
Gastro-retentive floating microspheres are low density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. Hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion / evaporation methods to prolong the gastric retention time (GRT) of the dosage form with continuously floating over the surface of an acidic dissolution media containing surfactant for >12 h

**METHODS OF PREPARATION:**
Some important methods to prepare microballoons are:

1. **Solvent Evaporation Method:**
   Floating multi particulate dosage form can be prepared by solvent diffusion and evaporation methods to create the hollow inner core. The polymer is dissolved in an organic solvent and the drug is either dissolved or dispersed in the polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing suitable additive (surfactants/polymer) to form oil in water emulsion. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring. The solvent removal leads to polymer precipitation at the oil/water interface of droplets, forming cavity and thus making them hollow to impart the floating properties. The polymers studied for the development of such systems include cellulose acetate, chitosan, Eudragit, Acrycoat, Methocil, polyacrylates, polyvinyl acetate, carbopol, agar, polyethylene oxide and polycarbonate.

2. **Emulsion Solvent Diffusion Method:**
   In the emulsion solvent diffusion method the affinity between the drug and organic solvent is stronger than that of organic solvent and aqueous solvent. The drug is dissolved in the organic solvent and the solution is dispersed in the aqueous solvent producing the emulsion droplets even though the organic solvent is miscible. The organic solvent diffuse gradually out of the emulsion droplets in to the surrounding aqueous phase by which drug crystallizes.
3. Spray Drying and Spray Congealing:
These methods are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively. The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer under high speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size ranges 1-100 µm. The spray drying process is used to encapsulate various penicillins.

2. LITERATURE REVIEW
V. Ganesan et al., (2013) researched on hollow microspheres (microballoons) of Telmisartan by emulsion solvent diffusion technique for sustained delivery by using polymers like Hydroxy Propyl Methyl Cellulose (HPMC) and Eudragit RS 100 in order to extend the drug release for about 12 h in the upper GIT, which may result in enhanced absorption and there by improved bioavailability. The particle size was determined by optical micrometer and average particle size was found to be in range of 189.5± 2.63 to 124.33± 2.14. Formulation F7 containing HPMC and Eudragit polymer blend showed the best floating ability (91.26%) as compared with other formulations. From Scanning Electron Microscopy (SEM) it was observed that, microspheres were found to be spherical in shape with smooth surface texture with a hollow space within. Among all formulations, F7 showed appropriate balance between buoyancy and drug release rate of 98.32% in 12 h, which is considered as the best formulation.

Suddhasatya Dey et al., (2011) investigated on design and characterization of floating microspheres with Nateglinide as model drug for prolongation of gastric residence time. Nateglinide Floating Microspheres were prepared by w/o/w emulsification solvent diffusion technique using rate controlling polymers ethyl cellulose and hydroxy propyl methyl cellulose. The shape and surface morphology of prepared microspheres were characterized by optical and scanning electron microscopy respectively. Effects of polymer concentration, solvent composition, particle size, drug entrapment efficiency and drug release were also observed. The prepared microspheres exhibited prolonged drug release (more than 12 h) and remained buoyant for &gt; 24 h. The mean particle size increased and the drug release rate decreased at higher polymer concentration. In vitro studies demonstrated diffusion- controlled drug release from the microsphere.

Dhyani Archana et al., (2016) reviewed on study on floating drug delivery system with special emphasis on microballoons as a drug delivery. Microballoons are emerging as the most promising drug delivery as it overcome many limitations of conventional drug delivery system. As microballoons delivery system provides longer retention in gastric pH, hence longer is the residence & therefore enhance the solubility of drugs that are less soluble in high pH environment, the formation of cavity inside the microsphere depends upon the preparation temperature & the surface smoothness determines the floatability and drug release rate of the microballoons.

N. Bhanu Priya et al., (2013) investigated on controlled release floating microballoons of pantoprazole using different polymers like HPMC, EC and gelatin for GRDDS along with the loading dose granules with super disintegrants. The immediate release (IR) granules were prepared by wet granulation method by using Sodium starch glycolate, Cross povidone as superdisintegrants and evaluated for the flow property and release studies. The granules showed good flowability and in vitro release of pantoprazole IR granules was found to be 96-102%. The floating microballoons were prepared by emulsion solvent diffusion method. The prepared microballoons were characterized for scanning electron microscopy (SEM), drug content, entrapment efficiency, production yield, floating ability, buoyancy percentage, in vitro drug release and release kinetics studies. SEM revealed that the microballoons had smooth surface and hollow cavity in the middle. The entrapment efficiency of microballoons was found to be 72-95% and the drug release from the microballoons in simulated gastric fluid (SGF) was found to be 54-68% up to 12 h. Thus it conclude that GRDDS of pantoprazole (an anti-ulcer drug) loaded microballoons along with IR granules loaded capsule was an ideal drug delivery system for ulcer protective activity as both controlled and immediate release drug delivery systems.

Peeyush Bhardwaj et al., (2010) researched on preparation and evaluation of floating microballoons of Indomethacin as a model drug, to increase its residence time in the stomach without contact with them ucosa. The microballoons were prepared by the emulsion solvent diffusion technique using different ratio of acrylic polymers (Eudragit RS100 and Eudragit S100) as carriers. The yield of microballoons was up to 91.02 ± 1.65%. Microballoons exhibited floating properties for more than 10 h. In vitro drug studies were performed in 0.1 M Hcl with 0.1% SLS and phosphate buffer (pH 6.2). Different drug release kinetics models were applied for selected batches.

Akash Yadav et al., (2012) investigated on sustained release gastro retentive microballoons of Metformin hydrochloride with the objective of improving its bioavailability Microballoons of Metformin hydrochloride were formulated by solvent evaporation and diffusion method using varying mixtures of hydroxypropyl methylcellulose (HPMC) and ethyl cellulose (EC) polymers. The balloons were characterized for particle size, surface morphology, incorporation efficiency, floating behavior and in vitro drug release. Release kinetic data showed best fit to the Higuchi model, indicating that diffusion was the predominant mechanism of drug release Microballoons is a potential suitable delivery system for sustained release of Metformin hydrochloride with improved bioavailability when compared with conventional dosage forms of the drug.

anddeep Yadav et al., (2015) researched on multiple unit dosage form as microballoons of a drug meant for management of hyperacidity using ranitidine hydrochloride employing poly vinyl alcohol (PVA), and Eudragit RS 100 as polymers by Quasi-emulsion solvent diffusion technique. Different batches of microballoons (F1 to F6) were prepared by varying the polymer ratios. With the increase in Eudragit concentration entrapment...
efficiency were increased which may be due to extended release property of polymer. The formulation F6 was selected as an ideal formulation based on entrapment efficiency and in vitro drug release tests. In vitro drug release was carried out in simulated gastric fluid (50 ml of 0.1N HCl) for 6 h by dialysis technique. The shape of microspheres demonstrated by scanning electron microscopy and found to be spherical. The drug release from the ideal formulation (F6) followed Higuchi model than the zero order kinetic models.

R. Senthil Prabhu et al., (2016) reviewed on microballoons is to accumulate the recent development on floatation to increase the gastric retention in the stomach and consequently, enhance that’s absorption and improve that’s bioavailability. Microballoons promises to be a potential approach for gastric retention time in the gastrointestinal tract (GIT). Microballoons were spherical in shape with porous smooth surface and good floating behavior. The microballoons exhibited prolonged drug release (8 hrs) and remained buoyant for >10hrs. The release rate was significantly affected by the type of combination and amount of the polymer used.

Peesh Singhal et al., (2011) investigated on formulate and develop a new gastro retentive sustained release delivery system of microballoons for Furosemide as model drug. Furosemide is a widely used high-ceiling loop diuretic drug with low bioavailability (60-70 %) and shorter half life (1-2 hrs). The microballoons were prepared by using o/w emulsion solvent evaporation method. The effect of various formulation and process variables on the internal and external particle morphology, micromeritic properties, invitro floating behavior (buoyancy), drug loading and invitro release were studied. The microballoons were found to be regular in shape. The microballoons remain buoyant (86.16±2.40) for 12 hrs. The optimized formulation (F4) was released approximately 81 % drug after 12 hrs. Invitro drug release followed the Higuchi model with diffusion mechanism and showed a biphasic pattern with an initial burst release.

Nilesh K. Gorde et al., (2013) reviewed on Microballoons (MB) a multiple unit dosage forms possessing a spherical cavity enclosed within a hard polymer shell have been develops as a dosage form characterize by excellent buoyancy in the stomach. This gastrointestinal transit-controlled preparation is design to float on surface of gastric juice, which has a specific gravity less than 1. Microballoons, loaded with drug in their outer polymer shells, prepare by the emulsion solvent diffusion method using enteric acrylic polymers; dissolve in a mixture of dichloromethane and ethanol. Dichloromethane evaporation appears to be especially related to cavity formation in microspheres. Microballoons incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs and floats continuously over the surface of acidic dissolution media containing surfactant for >12 h in vitro.

Adumbral Digambar Mali et al., (2015) reviewed on microballoons is to accumulate the recent literature with special focus on the recent development on floatation to achieve gastric retention. Microballoons are emerging as the most promising drug delivery as it overcome many limitations of conventional drug delivery system. As microballoons delivery system provides longer retention in gastric pH, hence longer is the residence time and therefore enhance the solubility of drugs that are less soluble in high pH environment. The formation of cavity inside the microsphere depends upon the preparation temperature and the surface smoothness determines the floatability and the drug release rate of the microballoons.

Kuldeep Patel et al., (2011) researched on Gastro retentive dosage forms have potential for use as controlled-release drug delivery systems. Multiple unit systems avoid the all-or-none gastric emptying nature of single-unit systems. A controlled release system designed to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of Microballoon delivery system by emulsion solvent diffusion method. The effect of various formulation and process variables on the internal and external particle morphology, Formulation demonstrated favourable in vitro floating and release characteristics. The drug encapsulation efficiency was high. Domperidone loaded microballoons proved desired release behavior and buoyancy. The designed system, combining excellent buoyant ability and suitable drug release pattern, could possibly be advantageous in terms of increased bioavailability of Domperidone loaded microballoons was found to be stable at various conditions.

Manas Tripathi et al., (2011) investigated on to formulate and evaluate the gastro-retentive floating microballoons of Glipizide using hydrophilic polymers hydroxypropyl methylcellulose (HPMC) and Eudragit RS100 (RS100) by emulsion solvent evaporation technique. The densities of floating microspheres (0.475-0.975 g/cm3) were found to be less than the density of gastric fluid (1.004 g/cm3), therefore showed an extended floating time of more than 12 h over the gastric fluid. The entrapment efficiency of prepared floating microspheres was satisfactory (41.32-76.19%). The scanning electron microscopy confirmed the hollow nature of microspheres with pores on the surface which imparted floating properties to the prepared floating microballoons. Among all formulations, F4 was found to be the best as it exhibited highest drug release (99.12%) in 12 h followed by diffusion mechanism and was stable for three months at ambient conditions.

3. AIM, OBJECTIVE & PLAN OF WORK

AIM AND OBJECTIVE:
The main aim of the present investigation was to prepare, characterize & evaluate the microballoons of Candesartan a poorly water soluble drug employing solvent evaporation method to approach, to formulate the Candesartan microballoons and to optimize the drug & carrier ratio using constant stabilizer concentration in the formulation of Candesartan microballoons.

PLAN OF WORK:
. construct the calibration curve of Candesartan using phosphate buffer of pH 7.4.
. PVP K30 as stabilizer and HPMC as carrier with solvent ratios are i.e. 1:2, 1:4 and 1:6. To prepare the microballoons of Candesartan by employing solvent method.
. To characterize the prepared microballoons for particle size analysis & SEM
To evaluate the practical yield, buoyancy, entrapment efficiency, drug content uniformity & in vitro dissolution rate of Candesartan microballoons.

4. DRUG AND EXCIPIENT PROFILE

4.1 Candesartan:

Chemical structure:

Name: Candesartan

Synonym: Candesartan cilexetil.

IUPAC Name:
2-ethoxy-3-[[4-[2-(2H-tetrazol-5-yl)phenyl]phenyl]methyl]benzimidazole-4- carboxylic acid

Mechanism of action:
Candesartan selectively blocks the binding of angiotensin II to AT1 in many tissues including vascular smooth muscle and the adrenal glands. This inhibits the AT1-mediated vasoconstrictive and aldosterone-secreting effects of angiotensin II and results in an overall decrease in blood pressure. Candesartan is greater than 10,000 times more selective for AT1 than AT2. Inhibition of aldosterone secretion may increase sodium and water excretion while decreasing potassium excretion.

Pharmacokinetics:
Absorption:
Candesartan cilexetil prodrug, the absolute bioavailability of candesartan was estimated to be 15%. Food with a high fat content has no effect on the bioavailability of candesartan from candesartan cilexetil.

Protein binding: >99%

Half life: Approximately 9 hrs

Volume of Distribution: 0.13 litre/kg.

Metabolism:
The prodrug candesartan cilexetil undergoes rapid and complete ester hydrolysis in the intestinal wall to form the active drug, candesartan. Elimination of candesartan is primarily as unchanged drug in the urine and, by the biliary route, in the feces. Minor hepatic metabolism of candesartan (<20%) occurs by O-deethylation via cytochrome P450 2C9 to form an inactive metabolite. Candesartan undergoes N-glucuronidation in the tetrazole ring by uridine diphosphate glucuronosyltransferase 1A3 (UGT1A3). O-glucuronidation may also occur. 75% of candesartan is excreted as unchanged drug in urine and feces

Elimination:
When candesartan is administered orally, about 26% of the dose is excreted unchanged in urine. Candesartan is mainly excreted unchanged in urine and feces (via bile).

Pharmacodynamics:
Candesartan blocks the vasoconstrictor and aldosterone secreting effects of angiotensinII by selectively blocking the binding of angiotensinII to AT1 receptor in many tissues.

Drug interaction:
- Warfarin
- Amphetamine

http://ijesc.org/
Hydro isoquinoline derivatives

Adverse effects:

- Headache
- Dizziness
- Cold or flu like symptoms
- Sore throat
- Nasal congestion

5. METHODOLOGY

1. EXPERIMENTAL STUDIES:

Preformulation testing is the first step in the rationale development of dosage form of a drug. It can be defined as an investigation of physical and chemical properties of drug substance, alone and when in combined with excipients.

SPECTROSCOPIC STUDIES:

Preparation of calibration curve of Candesartan:

100 mg of Candesartan was accurately weighed and transferred into 100ml standard flask and then volume was made up of 100ml with ethanol namely called as primary stock solution and from this takes 1ml of solution and dilute with 10ml of ethanol called as secondary stock solution. From the secondary stock solution, Pipette out 0.2ml, 0.4ml, 0.6ml, 0.8ml and 1ml transferred in to the 10ml standard flask and diluted to 10ml with phosphate buffer of pH 7.4 as shown in below.

<table>
<thead>
<tr>
<th>Volume (ml)</th>
<th>Solution Description</th>
<th>Absorbance Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>Diluted with phosphate buffer of pH 7.4 → 10ml → 2µg/ml</td>
<td>2µg/ml</td>
</tr>
<tr>
<td>0.4</td>
<td>Diluted with phosphate buffer of pH 7.4 → 10ml → 4µg/ml</td>
<td>4µg/ml</td>
</tr>
<tr>
<td>0.6</td>
<td>Diluted with phosphate buffer of pH 7.4 → 10ml → 6µg/ml</td>
<td>6µg/ml</td>
</tr>
<tr>
<td>0.8</td>
<td>Diluted with phosphate buffer of pH 7.4 → 10ml → 8µg/ml</td>
<td>8µg/ml</td>
</tr>
<tr>
<td>1.0</td>
<td>Diluted with phosphate buffer of pH 7.4 → 10ml → 10µg/ml</td>
<td>10µg/ml</td>
</tr>
</tbody>
</table>

Absorbance of the prepared solutions was determined spectrophotometrically at 290 nm, Phosphate buffer of pH 7.4 was used as blank. A graph was plotted with concentration of Candesartan (µg/ml) on X-axis against absorbance on y-axis. (Dhyani archana)

PREPARATION AND CHARACTERIZATION OF MICROBALLOONS OF CANDESARTAN:

Preparation of Microballoons:

In the present study, microballoons of Candesartan were prepared by Solvent evaporation method in which the polymer and solvent ratio has been optimized.

Solvent evaporation method:

Accurately weighed amount of drug and polymer was mixed with 20 ml of acetone in a beaker. The solution was stirred for 10 minutes. This solution was poured drop wise drop to 0.5% w/v of PVA solution. Add 0.5 % Tween 40 to the solution. The resultant solution was kept under a mechanical stirrer at a constant speed of 400 rpm for 2 hours. The micro balloons were formed and they can be washed, filtered through what man filter paper, collected and dried in hot air oven at 60°C. [N. Bhanu Priya] [Akash Yadav] [Mankala SK]

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Candesartan (g)</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>2.</td>
<td>PVP K30(g)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>3.</td>
<td>HPMC</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
</tr>
<tr>
<td>4.</td>
<td>Acetone + dichloromethane (ml)</td>
<td>20</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>5.</td>
<td>Distilled water(ml)</td>
<td>20</td>
<td>40</td>
<td>60</td>
</tr>
</tbody>
</table>

Table 1. Composition of Different Formulations of Candesartan Microballoons

EVALUATION OF CANDESARTAN MICROBALLOONS:

Prepared microballoons were evaluated for the following parameters:

- Percentage practical yield
- % Buoyancy test
- % Entrapment efficiency
- % Drug content
- In vitro dissolution studies

Particle size analysis: (optical microscopy)

The eye piece micrometer was calibrated by using a standard stage micrometer at 45X. Samples were taken and the suspension was prepared by using propylene glycol and the prepared suspension was mounted on a slide and placed on a mechanical stage. The size of particles was estimated with the help of eye piece micrometer. Around 50 particles were counted to estimate the true mean and the results are tabulated. [Chowdary KPR]

SCANNING ELECTRON MICROSCOPY (SEM):

Scanning electron micrographs of Candesartan microballoons and pure drug powder were taken using a scanning electron microscope (Philips, Philips XL 30 ESEM, and Japan). Samples were fixed on an aluminium stub with conductive double-sided adhesive tape and coated with gold in an argon atmosphere (50 Pa) at 50mA for 50 sec and the results are depicted. [Nilesh K]
6. RESULTS & DISCUSSION

1. SPECTROSCOPIC STUDIES:

*STANDARD CALIBRATION CURVE OF CANDESARTAN:

Table 2. Standard curve data of Candesartan using phosphate buffer of pH 7.4

<table>
<thead>
<tr>
<th>S. No</th>
<th>Concentration (µg/ml)</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>2</td>
<td>0.167</td>
</tr>
<tr>
<td>2.</td>
<td>4</td>
<td>0.323</td>
</tr>
<tr>
<td>3.</td>
<td>6</td>
<td>0.481</td>
</tr>
<tr>
<td>4.</td>
<td>8</td>
<td>0.661</td>
</tr>
<tr>
<td>5.</td>
<td>10</td>
<td>0.811</td>
</tr>
</tbody>
</table>

Figure 7. Standard plot of Candesartan in phosphate buffer of pH 7.4

Absorbance: In the present study, analytical method obeyed the beer-lamberts law in the concentration range of 2-10 µg/ml and was suitable for the estimation of Candesartan using phosphate buffer of pH 7.4. The linear regression equations were used for the estimation of selected drug from phosphate buffer of pH 7.4.

*EVALUATION OF CANDESARTAN MICROBALLOONS:

% PRACTICAL YIELD:

Table 3. % practical Yield of Candesartan microballoons

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Formulation Code</th>
<th>% Practical yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>F₁</td>
<td>87.3%</td>
</tr>
<tr>
<td>2.</td>
<td>F₂</td>
<td>98.4%</td>
</tr>
<tr>
<td>3.</td>
<td>F₃</td>
<td>91.1%</td>
</tr>
</tbody>
</table>
Percentage practical yield of Candesartan microballoons containing PVP K30 as stabilizing agent & HPMC as a carrier were in the range of 87.3% - 91.1% as shown in above Table. The percentage practical yield was low for F1 and the high for F2. Higher practical yield 98.4% was obtained in case of Candesartan microballoons prepared by using PVP & HPMC at solvent (v/v) ratio of 1:4.

**% BUOYANCY TEST:**

<table>
<thead>
<tr>
<th>S. No</th>
<th>Formulation Code</th>
<th>% Buoyancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>F1</td>
<td>66.04</td>
</tr>
<tr>
<td>2.</td>
<td>F2</td>
<td>77.71</td>
</tr>
<tr>
<td>3.</td>
<td>F3</td>
<td>71.01</td>
</tr>
</tbody>
</table>

Percentage buoyancy of Candesartan microballoons containing PVP K30 as stabilizing agent & HPMC as a carrier were in the range of 66.04% - 77.71% as shown in above Table. The percentage buoyancy was low for F1 and the high for F2 (ratio of 1:4).

**% ENTRAPMENT EFFICIENCY:**

<table>
<thead>
<tr>
<th>S. No</th>
<th>Formulation Code</th>
<th>% Entrapment efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>F1</td>
<td>81.01</td>
</tr>
<tr>
<td>2.</td>
<td>F2</td>
<td>82.09</td>
</tr>
<tr>
<td>3.</td>
<td>F3</td>
<td>79.36</td>
</tr>
</tbody>
</table>

All the three formulations showed satisfactory entrapment efficiency ranging in 81.01 to 79.36 and F3 showed efficiency slightly decreased with increasing the HPMC. F2 showed highest % entrapment efficiency.

**% DRUG CONTENT ESTIMATION:**

<table>
<thead>
<tr>
<th>S. No</th>
<th>Formulation Code</th>
<th>% Drug content</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>F1</td>
<td>89.21</td>
</tr>
<tr>
<td>2.</td>
<td>F2</td>
<td>97.01</td>
</tr>
<tr>
<td>3.</td>
<td>F3</td>
<td>93.22</td>
</tr>
</tbody>
</table>

The percent drug content of Candesartan microballoons in the range of 89.21 - 93.22 as shown in above Table. It was low for F1 and the high for F2 (97.01). The results revealed that the ratios and carriers used to prepare formulations have shown no effect on the drug content and uniformity of the microballoons.

**IN VITRO DISSOLUTION STUDIES:**

<table>
<thead>
<tr>
<th>SNO</th>
<th>TIME (min)</th>
<th>% CUMULATIVE DRUG RELEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PURE DRUG</td>
</tr>
<tr>
<td>1.</td>
<td>15</td>
<td>14.31</td>
</tr>
<tr>
<td>2.</td>
<td>30</td>
<td>27.22</td>
</tr>
<tr>
<td>3.</td>
<td>45</td>
<td>41.04</td>
</tr>
<tr>
<td>4.</td>
<td>60</td>
<td>52.77</td>
</tr>
</tbody>
</table>

* IN VITRO DISSOLUTION STUDIES:

<table>
<thead>
<tr>
<th>SNO</th>
<th>TIME (min)</th>
<th>% CUMULATIVE DRUG RELEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PURE DRUG</td>
</tr>
<tr>
<td>1.</td>
<td>15</td>
<td>14.31</td>
</tr>
<tr>
<td>2.</td>
<td>30</td>
<td>27.22</td>
</tr>
<tr>
<td>3.</td>
<td>45</td>
<td>41.04</td>
</tr>
<tr>
<td>4.</td>
<td>60</td>
<td>52.77</td>
</tr>
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</table>
In vitro dissolution profiles of Candesartan microballoons were prepared by solvent evaporation method were compared with that of the pure Candesartan. All formulations viz. F1-F3 have shown increased cumulative dissolution profiles in comparison with that of pure drug as shown above. From the results, it was found that the percentage drug release of pure drug was low and only 52.77 were dissolved within 60 minutes. Out of three formulations (F1-F3) prepared, F2 formulation containing PVP k30 as stabilizing agent with HPMC as a carrier i.e., 98.45 of highest % drug release. From the results, it was revealed that the F2 showed enhancement in dissolution rate of microballoons occurs due to the presence of PVP k30 & HPMC. Finally the ratio of polymer: solvent range of F2 is optimized and also it exists highest % drug release.

* CHARACTERIZATION OF CANDESARTAN MICROBALLOONS:

PARTICLE SIZE ANALYSIS: (OPTICAL MICROSCOPY)

Table 8. Mean particle size of Candesartan microballoons

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Formulation Code</th>
<th>Mean particle size (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Pure drug</td>
<td>72.41</td>
</tr>
<tr>
<td>2.</td>
<td>F1</td>
<td>28.63</td>
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<tr>
<td>3.</td>
<td>F2</td>
<td>23.03</td>
</tr>
<tr>
<td>4.</td>
<td>F3</td>
<td>26.10</td>
</tr>
</tbody>
</table>

The mean particle size of untreated Candesartan powder was 80 µm while particles precipitated in the presence of PVPK30 & HPMC was less than 30 µm. The above results revealed optimized formulation (F2) showed less particle size compared to F1 & F3.

SCANNING ELECTRON MICROSCOPY (SEM):

Figure 9. SEM of Pure Candesartan.

Scanning electron micrographs of pure Candesartan drug powder and Candesartan microballoons were shown in above. Pure Candesartan powder showed large shaped crystal habit (103 µm) and F2 showed small round shaped crystals (25 µm).
7. CONCLUSION

The Candesartan microballoons were prepared by using PVPk30 as a stabilizer & HPMC is a carrier with specific ratio of solvents (Acetone & water). The results were obtained from in vitro dissolution data revealed that the prepared Candesartan microballoons (F2) were having good buoyancy and entrapment efficiency. It was further concluded that with the variation in concentration of polymer, microballoons of different size, % practical yield and drug content can be obtained with satisfactory results. Microballoons were prepared by using solvent evaporation method, F2 is optimized formulation & it showed highest percentage drug release. SEM results were also showed compared to pure drug the F2 consists of round shaped less particle size (25µm). So, it can be concluded that microballoons drug delivery system can be used as gastro retentive drug delivery system and the mentioned technique is a promising tool for effective microballoons formation.

8. REFERENCES