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Research article ***Pharmaceutical Science***

Enhancement of solubility and preparation of oral thin film of candesartan using various polymers

Subhankar Khan*, Mithun Bhowmik, Pratibha Bhowmick

Bengal College of Pharmaceutical Sciences and Research, Durgapur, West Bengal, India

***Corresponding Author: Subhankar Khan**
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ABSTRACT

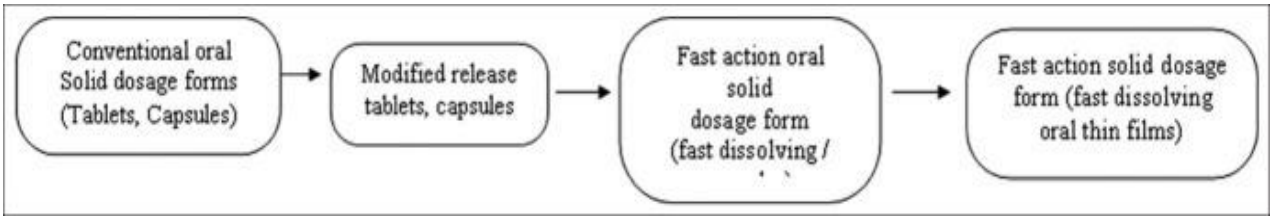
The objective of the present study was to develop mouth dissolving films (MDF) of Candesartan for the treatment of high blood pressure and congestive heart failure, with fast disintegration, optimum morphological properties, and mechanical strength. Candesartan is an anti-hypertensive drug which undergoes extensive first-pass metabolism that results in low bioavailability of the drug. Through buccal route, the drug directly enters blood circulation and hence bioavailability of the drug increases. Carbopol, PectinandTragacanth were used as the film-forming polymeric bases and Poly propylene glycol as plasticizer. Films were prepared by solvent casting technique. Parameters like *in-vitro* disintegration time, tensile strength, content uniformity, folding endurance and *in-vitro* drug release were evaluated. *In-vitro* dissolution studies showed that 99.46% of Candesartan was released within 30 min with an average disintegration time of 12 sec. FTIR spectrophotometry were used to identify drug-excipient interactions.
The formulation developed is simple, easy to prepare and economical with great applicability during the emergency cases such as Hypertension, whenever immediate onset of action is desired.

Keywords: Candesartan, Carbopol, Pectin, Tragacanth and solvent casting method.

INTRODUCTION

The oral route is one of the most preferred routes of drug administration as it is more convenient, cost effective, and ease of administration lead to high level of patient compliance. The oral route is problematic because of the swallowing difficulty for pediatric and geriatric patients who have fear of choking. Patient convenience and compliance oriented research has resulted in bringing out safer and newer drug delivery systems. Recently, fast dissolving drug delivery systems have started gaining popularity and acceptance as one such example with increased consumer choice, for the reason of rapid disintegration or dissolution, self-administration even without water or chewing. Fast dissolving drug delivery systems were first invented in the late 1970s as to overcome swallowing difficulties associated with tablets and capsules for pediatric and geriatric patients. Buccal drug delivery has lately become an important route of drug administration. Various bioadhesive mucosal dosage forms have been developed, which includes adhesive tablets, gels, ointments, patches, and more recently the use of polymeric films for buccal delivery, also known as mouth dissolving films. The surface of buccal cavity comprises of stratified squamous epithelium which is essentially separated from the underlying tissue of lamina propria and submucosa by an undulating basement membrane.[1,2] It is interesting to note that the permeability of buccal mucosa is approximately 4-4,000 times greater than that of the skin, but less than that of the intestine.[3] Hence, the buccal delivery serves as an excellent platform for absorption of molecules that have poor dermal penetration.[4] The primary barrier to permeability in otiral mucosa is the result of intercellular material derived from the so-called 'membrane coating granules' present at the uppermost 200 µm layer.[5] These dosage forms have a shelf life of 2-3 years, depending on the active pharmaceutical ingredient but

are extremely sensitive to environmental moisture.[6] An ideal fast dissolving delivery system should have the following properties: High stability, transportability, ease of handling and administration, no special packaging material or processing requirements, no water necessary for application, and a pleasant taste. Therefore, they are very suitable for pediatric and geriatric patients; bedridden patients; or patients suffering from dysphagia, Parkinson's disease, mucositis, or vomiting. This novel drug delivery system can also be beneficial for meeting current needs of the industry. Rapidly dissolving films (RDF) were initially introduced in the market as breath fresheners and personal care products such as dental care strips and soap strips. However, these dosage forms are introduced in the United States and European pharmaceutical markets for therapeutic benefits. The first of the kind of oral strips (OS) were developed by the major pharmaceutical company Pfizer who named it as Listerine® pocket packs™ and were used for mouth freshening. Chloraseptic relief strips were the first therapeutic oral thin films (OTF) which contained[7] benzocaine and were used for the treatment of sore throat. Formulation of fast dissolving buccal film involves material such as strip-forming polymers, plasticizers, active pharmaceutical ingredient, sweetening agents, saliva stimulating agent, flavoring agents, coloring agents, stabilizing and thickening agents, permeation enhancers, and superdisintegrants. All the excipients used in the formulation of fast dissolving film should be approved for use in oral pharmaceutical dosage forms as per regulatory perspectives.



Advantages

- Oral films have some special advantages over other oral dosage forms given as follows:
- Rapidly dissolved and disintegrated in the oral cavity because of large surface area which lowers dosage interval, improves onset of action, efficacy and safety profile of therapy.
- Oral films are more flexible, compliant and are not brittle as ODTS.
- Easily handled, storage and transportation.
- Accuracy in the administered dose is assured from every strip or film.
- Pharmaceutical companies and customers practically accepted OTFs as an alternative of conventional OTC dosage forms such tablets and capsules etc. (Frey, 2006).
- Oral film is desirable for patient suffering from motion sickness, dysphagia, repeated emesis and mental disorders.
- From commercial point of view, oral films provide new business opportunity like product differentiation, promotion etc.[8,9]

Disadvantages

The main disadvantage of this delivery system is we cannotincorporate high dose into strip or film. Novartis consumerhealth's Gas-x thin strip has loaded 62.5mg of simethiconeperstrip but there remain number oflimitations with the use of film strips.[10]

Ideal Characteristics of a Suitable Drug Candidate [11]

- The drug should have pleasant taste.
- The drug to be incorporated should have low dose up to 40 mg.
- The drug should have smaller and moderate molecular weight.
- The drug should have good stability and solubility in water as well as saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have ability to permeate the oral mucosal tissue.

Classification of oral films

There are three types of oral films:

1. Flash release
2. Mucoadhesive melt away wafer
3. Mucoadhesive sustained release wafers

Applications of oral films in drug delivery

- Oral drug delivery by sublingual, mucosal and buccal become preferable for therapies in which immediate absorption is required including those used to manage pain, allergies, sleep problems and CNS disorders.
- **Topical applications,** the oral films are ideal in the delivery of active agents like analgesic or antimicrobial ingredients for the care of wound and other applications.
- **Gastroretentive dosage systems**, poorly soluble and water soluble moleculesof different molecular weights are found in film format [12].
- Dissolution of oral films could be initiated by the pH or enzymatic secretion of GIT and are used to treat gastrointestinal disorders.
- **Diagnostic devices**, Oral films loaded with sensitive reagent to allow controlled release faced to biological fluid for separating multiple reagents to allow a timed reaction within diagnostic device.[13]

Film Forming Polymers[14]

A variety of polymers are available for preparation of fast dissolving oral films. The use of film forming polymers in oral films has attracted considerable attention in medical and nutraceutical applications. The selection of film forming

polymers, is one of the most important and critical parameter for the successful development of film formulation. The polymers can be used alone or in combination to provide desired film properties. The polymers used in oral film formulation should be:

- Nontoxic and nonirritant.
- Devoid of leachable impurities.
- Should not retard disintegration time of film.
- Tasteless.
- Should have good wetting and spread ability property.
- Should have sufficient peel, shear, and tensile strength.
- Readily available.
- Inexpensive.
- Sufficient shelf life.
- Should not aid in causing secondary infections in oral mucosa.

Presently, both natural and synthetic polymers are used for the preparation of orally dissolving films. represent various natural and synthetic polymers used for preparation of fast dissolving films. represent the quality parameters of natural and synthetic polymers, respectively.

MATERIALS

Candesartan Provided by SURA LABS, Dilsukhnagar, Hyderabad, CarbopolFisher Scientific, India, Pectin Morepenlabsltd,Parwanoo(HP), India, Tragacanth PraavarChemtech, Mumbai, Poly propylene glycol (mL) Millipore system, D.WS.d.fine chem. Ltd, Mumbai, India.

METHODOLOGY

Drug –Polymer compatibility studies by FT-IR

Drug polymer compatibility studies were performed by FT-IR (Fourier transform infrared spectroscopy). In order to confirm that the entrapment of drug within the polymeric systems involve only the physical process and no interaction between drug and polymer. FTIR absorption Spectra's were shows no significant interaction between drug and polymers.

Selection of the drug

- The Candesartan which has significantly different pharmacokinetic profiles.
- Candesartan is a drug that breaks up phlegm, used in the treatment of respiratory diseases associated with viscid or excessive mucus. Ambroxol is often administered as an active ingredient in cough syrup.
- Candesartan was soluble in water and in solvents.
- Candesartan was stable at salivary pH.

Construction of calibration curve for Candesartan
Determination of λmax

Candesartan λmax was determined by spectrophotometer using pH 6.8 buffer medium. First dissolve 10mg of pure drug in 10ml of 6.8 buffer medium. From this 10µg/ml solution was prepared by using 6.8 buffer. 10µg/ml solution absorbance was measured at 200-400 nm range by spectrophotometrically using 6.8 buffer as reference solution.

Preparation of calibration curve

1. **Primary stock solution:** Standard calibration curve of Candesartan in 6.8 buffer were prepared. First dissolve 10mg of pure drug in 10ml of 6.8 buffers this is primary stock solution.
2. **Second stock solution:** From the above primary stock solution pipette out 1ml of solution and again make up to 10ml this is secondary stock solution. From this secondary stock solution different concentrations of Candesartan (2, 4, 6, 8, and 10 µg/ml) in 6.8 buffers were prepared and absorbance of these solutions measured at 255 nm by spectrophotometrically using 6.8 buffer as reference solution.

Preparation of mouth dissolving films
General method of formulation of oral dissolving films

Following processes are generally used to manufacture the mouth dissolving film.

1. Solvent casting
2. Semisolid casting
3. Hot melt extrusion
4. Solid dispersion extrusion
5. Rolling method

The current preferred manufacturing process for making this film is solvent casting method. In this method water soluble polymer is dissolved in suitable solvent to make homogenous viscous solution. In this other excipients (plasticizer and sweetner) including drug resinate complex were dissolved under stirring. Then the solution is degassed by keeping it in the sonicator. The resulting bubble free solution poured into petriplate and was kept in oven. Dried film is then cut into the desired shape and size for the intended application.

Preparation of blank films using different polymers

- Accurately weighed quantity of polymer was dissolved in specific quantity of water.
- The dissolved polymer was made to a uniform dispersion using a homogenizer.
- During stirring other excipients (plasticizer and sweetner) were added.
- Then the solution is degassed by keeping it in the Sonicator.
- The bubble free solution poured into petriplate and was kept in oven.
- Then the dried films were used to select the best film forming polymers.

Selection of best film forming polymer

The polymer employed should be non-toxic, non-irritant and devoid of leachable impurities. It should have good wetting and spreadability property. The polymer should exhibit sufficient peel, shear and tensile strengths. The polymer should be readily available and should not be very expensive. Film obtained

should be tough enough to avoid the damage while handling or during transportation.

Different Polymers Used For Trails

- Carbopol
- Pectin
- Tragacanth

Preparation of oral fast dissolving film

Oral fast dissolving film was prepared by solvent casting method. Aqueous solution I was prepared by dissolving film forming polymer, in specific proportion in distilled water and allowed to stirred for 3 hours and kept for 1 hour to remove all the air bubble entrapped or remove bubbles. Aqueous solution II was prepared by dissolving the pure drug, sweetener, and plasticizer in specific proportion in distilled water.

Formulation of Candesartan oral fast dissolving films

Table 1: Composition of Candesartan oral dissolving films

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Candesartan	4	4	4	4	4	4	4	4	4
Carbopol	20	40	60	-	-	-	-	--	-
Pectin	-	-	-	20	40	60	-	-	-
Tragacanth	-	-	-	-	-	-	20	40	60
Poly propylene glycol (mL)	2.5	2.5	2.5	5	5	5	7.5	7.5	7.5
D.W	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Sodium starchglycolate	10	20	30	40	-	-	-	-	-
Croscarmellose sodium	-	-	-	-	10	20	30	40	50
Aspartame	10	10	10	10	10	10	10	10	10
Total weight	80	80	80	80	80	80	80	80	80

RESULTS AND DISCUSSION

Analytical Method Development forCandesartan

Construction of Calibration Curve

Candesartan λ_{max} was determined by spectrophotometer using pH 6.8 buffer medium. First dissolve 10 mg of pure drug in 10 ml of 6.8 buffer medium. From this 10 µg/ml solution was prepared by using 6.8 buffer, 10 µg/ml solution absorbance was scanned at 200 to 400 nm range by spectrophotometrically using pH 6.8 buffer as reference solution and λ_{max} was observed at 255 nm. A standard graph of pure drug in suitable medium was prepared by plotting the concentration (µg/ml) on X-Axis and absorbance on Y-Axis. An excellentcorrelationco-efficient (R^2=0.998) was observed.

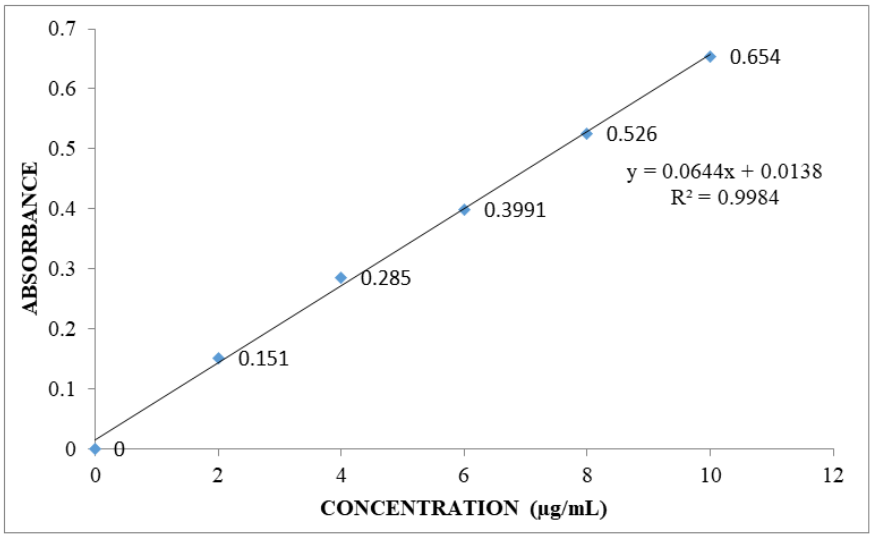


Fig1: Calibration curve of Candesartan in pH 6.8 phosphate buffer at λ_{max} =255 nm

Drug-Excipient Compatibility (FTIR studies)

IR spectral analysis was carried out using FT-IR and the results showed that there were no interactions between drug and Excipients.

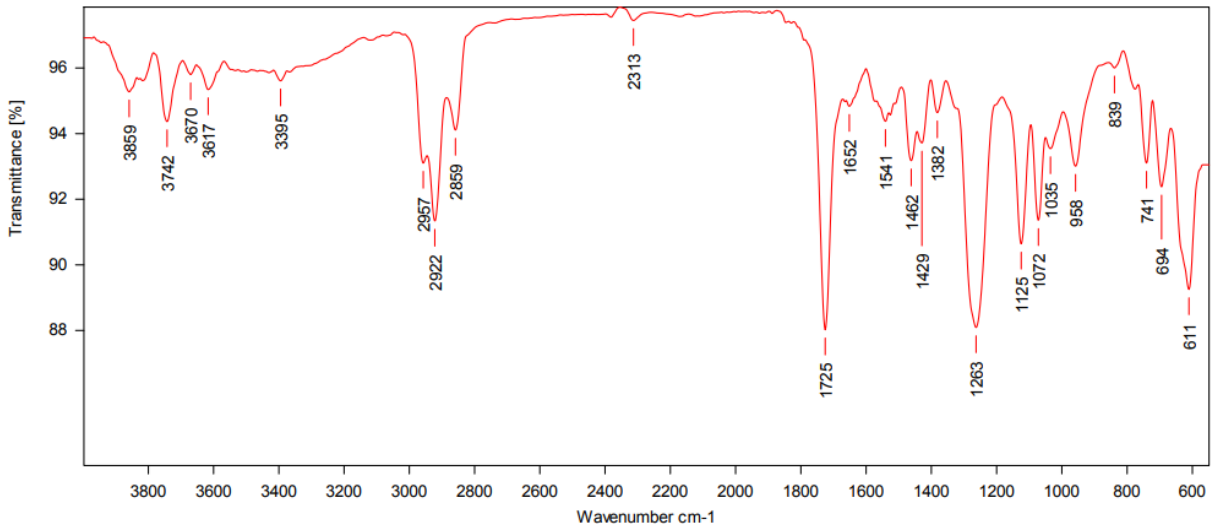


Fig 2: Candesartan Pure Drug FTIR

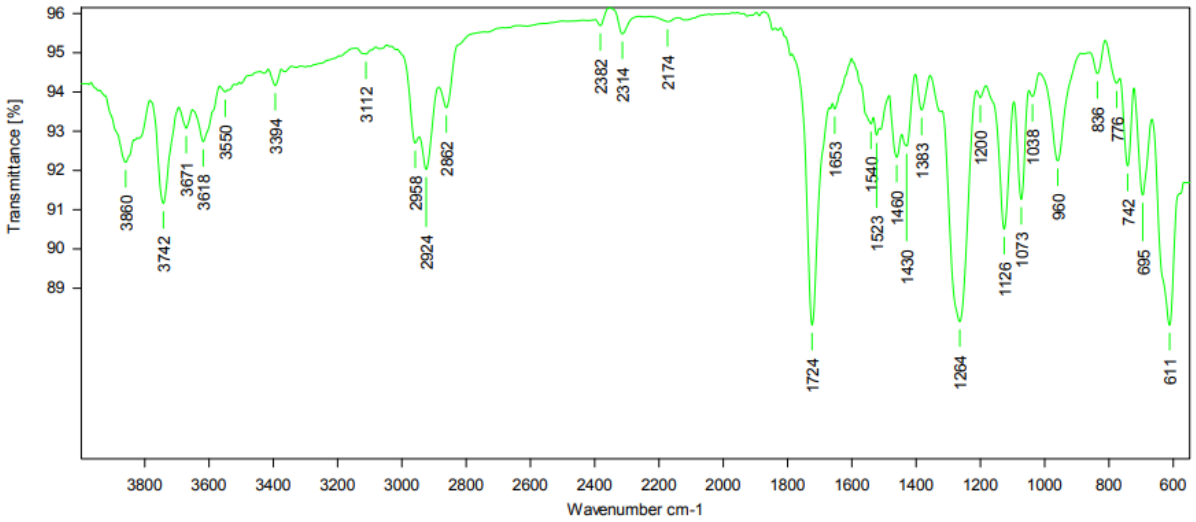


Fig3: Candesartan Optimised Formulation FTIR

Table2: Physical evaluation parameters of all formulations

Formulation Code	Thickness (mm)	Weight Variation (mg)	Disintegration Time(sec)	Drug content (%)	Tensile Strength (g/cm^2)	% Elongation	Folding Endurance (Count)
F1	1.35	99	21	97.32	5.3	3	61
F2	1.56	98	18	98.14	5.9	5	68
F3	1.47	97	15	98.34	6.1	6	73
F4	1.62	100	12	99.61	6.2	8	79
F5	1.30	98	26	98.67	4.9	4	53
F6	1.28	99	23	97.94	5.2	6	57
F7	1.49	99	19	98.60	5.6	6	65
F8	1.62	97	16	99.76	5.9	5	68
F9	1.58	100	14	98.14	6.1	6	72

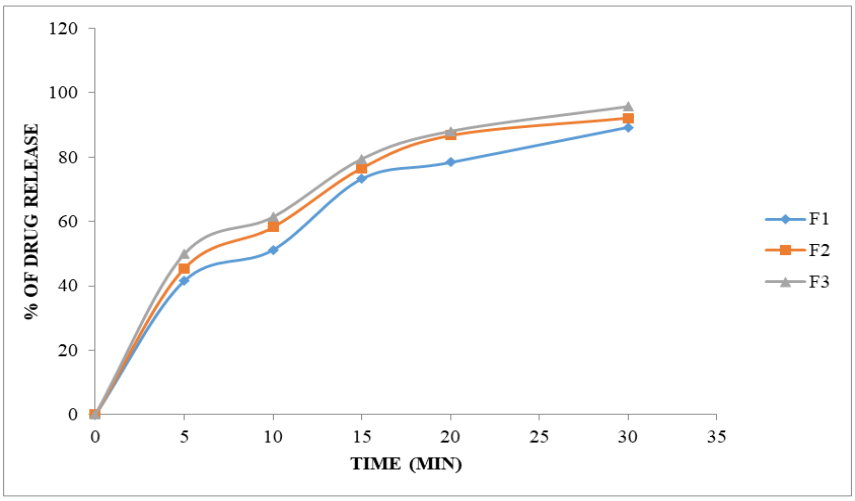


Fig4: Comparison curve of *Invitro* drug release for F1-F3 formulations

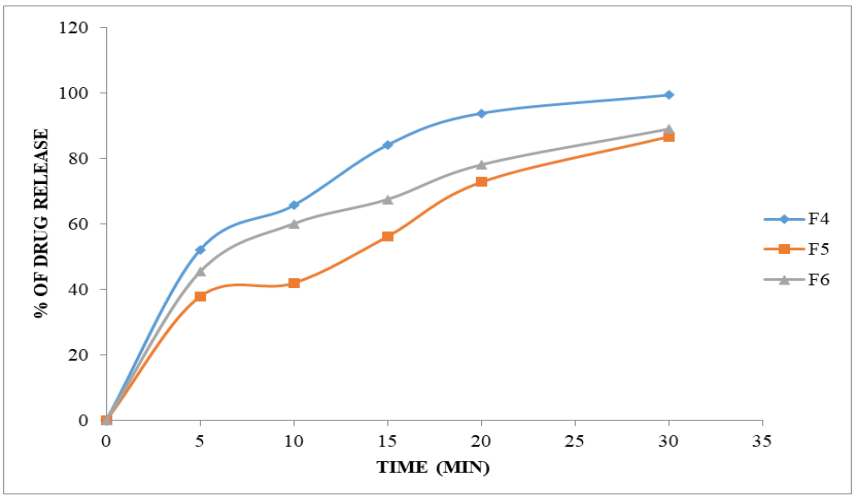


Fig 5: Comparison curve of *Invitro* drug release for F4- F6 formulations

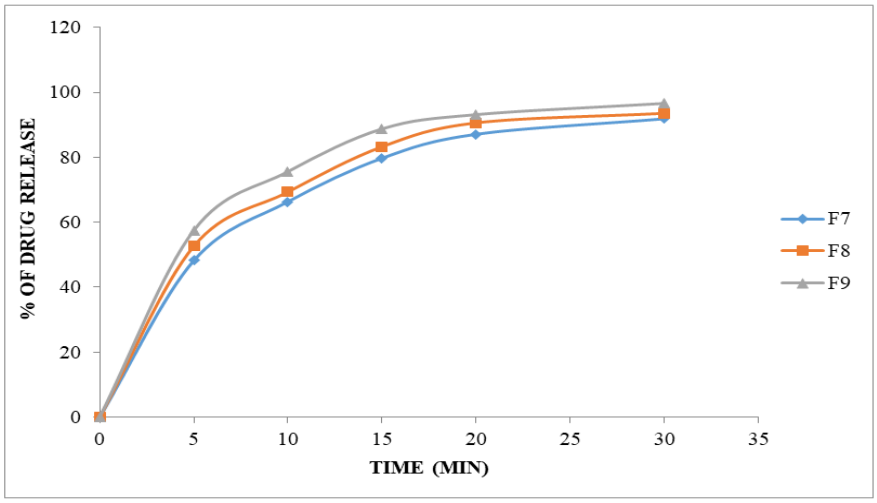


Fig 6: Comparison curve of *Invitro* drug release for F7- F9 formulations

DISCUSSION

Analytical method development for Candesartan λ max determination

λ max determination of Candesartan pH 6.8 phosphate buffer was determined by using UV Spectrophotometer at 255 nm.

Development of standard graph

Standard plot of Candesartan pH 6.8 phosphate buffer were plotted to concentration vs absorbance at 255 nm and the slope value and R^2 value were found to be 0.998.

Evaluation properties

The different Candesartan film formulations were evaluated for mechanical properties like thickness, drug content uniformity, folding endurance, tensile strength, weight uniformity, disintegration time, *in vitro* dissolution studies.

Thickness

The thickness of the films from F1-F9 formulations were ranged from 1.28 to 1.62. F4formulation had the maximum thickness values in all the formulations. From the thickness values it is concluded that as the polymer concentration increases, thickness also increased.

Tensile strength& Percentage elongation

The tensile strength of the films from F1-F9 formulations were ranged from 5.3 to 6.2 kg. F4 formulation had the maximum tensile strength and. From the tensile strength values it is concluded that as the polymer concentration increases, tensile strength and percentage elongation also increased.

Drug content uniformity

The drug content uniformity of the films from F1-F9 formulations were ranged from 97.32% to 99.61 %. F4 formulation had the maximum drug content uniformity.

Folding endurance

The folding endurance value of the films from F1-F9 formulations were ranged from 61 to 79. In Pectin containing formulations as polymer concentration low folding endurance values were more.

Weight uniformity

Weight uniformity of films were carried out for all the formulations and weight variation varies from 97to 100 mg.

Disintegration time

The disintegration time is the time when a film starts to break or disintegrate. The *in vitro* disintegration time was calculated for all the formulations and it ranges from 12 sec to26 sec Disintegration time of the films was increased with increase in concentration of the disintegrants, as more fluid is required to wet the film in the mouth. F4 formulation was quickly disintegrated that is in 12sec.

Finally selection of the best formulation from all the formulations was carried by using *In Vitro* dissolution studies.

In vitro dissolution studies

In vitro dissolution study of F1-F9 formulations were showed different drug release of 89.28 %, 92.17 %, 95.75% and 99.46 %,respectively within 30min. Among the formulations F4showed good dissolution property hence it is optimized and it contains 25 mg of Pectin as film forming polymer.

Small differences were observed in dissolution of drug from the different formulations of the film. Present study reveals that maximum all formulated films showed satisfactory film parameters. Among the optimized formulations F4formulation showed better drug release of 99.46%within30 min. F4 formulation contains 20mg of Pectin polymer as film forming agent. Compared with among Carbopol and Tragacanthformulationshave good disintegration property which enables good dissolution of the formulations.So, it is assumed that 20 mg Pectin containing oral fast dissolving film was optimized in which it showed a drug release of 99.46%compared with other batch formulations.

CONCLUSION

BCS class II drugs need the enhancement of the solubility thereby bioavailability, hence different techniques have been explored for the enhancement of the oral bioavailability. In the present study, it was studied the effect of polymers and superdisintegrants observed that, improved the solubility of Candesartan by formulating the Oral Fast Dissolving Films having different concentrations of film formers indicated that all the prepared formulations were having the physical and chemical properties. Based on the results of all the formulations, optimized formulations have confirmed the improvement in the solubility of formulations were prepared by using similar formula with omitting Pectinand Sodium starchglycolate in the formulation. The results clearly indicated that, the influence of Sodium starchglycolate in optimized formulations shown complete drug release within 4 min, whereas only 52.09% of drug release observed after 30 min in the formulation drug release observed 99.46%. Hence the effect of polymers and superdisintegrants was clearly established.

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