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FORMULATION AND IN-VITRO EVALUATION OF BENAZEPRIL MOUTH DISSOLVING FILMS

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Abstract:
Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients. But oral drug delivery systems still need some advancement to be made because of their some drawbacks related to particular class of patients which includes geriatric, pediatric and dysphasic patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms. The aim of this is to highlight the potential role of fast dissolving drug delivery in achieving effective drug delivery of antihypertensive drug. It gives rapid absorption and instant bioavailability of drugs due to high blood flow. As the fast-dissolving film is taken through the sublingual route, rapid absorption of drug is possible, which finally leads to quick onset of drug action and prevent the first pass-metabolism of the drug. Preformulation studies were done with benazepril(API),polymers were HPMC E5,HPME E3LV,HPME 5CPS,film forming polymer and disintegrate as maltodextrin, plasticizer as PEG, sweetener as aspartame, cooling agent as mannitol,colouring agent as amaranth, salivating agent as citric acid. For above formulations evaluation parameters are (appearance, thickness uniformity, weight uniformity, drug content uniformity, folding endurance, surface pH of film, in vitro disintegration time, in vitro dissolution studies) were placed in pH 1.2(0.1N HCL) and the drug release were conducted. Kinetic data of optimized drug is conducted (zero order kinetics, first order kinetics, Higuchi model, Korsmeyer–Peppas model). Drug was released from the formulation F8 within 9 minutes. Based on the physico-mechanical properties and in-vitro drug release.

Keywords: *Anti-hypertensive, benazepril, HPMC E5, HPME E3LV, HPME 5CPS, PEG, pH 1.2, higuchi model, Korsmeyer- peppas model*

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INTRODUCTION:

Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients. But oral drug delivery systems still need some advancement to be made because of their some drawbacks related to particular class of patients which includes geriatric, pediatric and dysphasic patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take solid preparations due to fear of choking. Fast dissolving drug-delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for pediatric and geriatric patients who experience difficulties in swallowing traditional solid-dosage forms. These systems consist of the solid dosage forms that disintegrate and dissolve quickly in the oral cavity without the administration of water. Research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets or capsules to modified release tablets or capsules to oral disintegrating tablet (ODT) to wafer to the recent development of oral fast dissolving films (OFDFs). Amongst the plethora of avenues explored for the rapid drug releasing products, oral strip technology is gaining much attention **[1, 2]**. The aim of this is to highlight the potential role of fast dissolving drug delivery in achieving effective drug delivery of antihypertensive drug. Furthermore, the concept of a fast dissolving drug delivery is reviewed and discussed

The work is aimed to develop and optimize fast dissolving oral films of Benazepril to ensure satisfactory drug release with the help of polymers and thereby avoid first pass metabolism, enhance bioavailability and rapid onset of action .There has been increased demand for the novel dosage form to gain more patient compliance. Fast dissolving films recently have acquired great importance in the pharmaceutical industry due to their unique properties and specific advantages like no need of water for disintegration, accurate dosing, and rapid onset of action, ease of transportability, ease of handling, pleasant taste and improved patient compliance. Fast dissolving film is a type of drug delivery system, which when placed in the oral cavity it rapidly disintegrates and dissolves to release the medication for or mucosal and intra gastric absorption, without chewing and intake of water. These films have a potential to deliver the drug systemically through intra gastric, sublingual or buccal route of administration and has been used for local action. It gives rapid absorption and instant bioavailability of drugs due to high blood flow. As the fast-dissolving film is taken through the sublingual route, rapid absorption of drug is possible, which finally leads to quick onset of drug action and prevent the first pass-metabolism of the drug **[3]**.

MATERIALS AND METHODS:

Materials:

Benazepril purchased from Dr. Reddy's Lab's, Hyderabad, HPMC E5, HPME E3LV, HPME 5 CPS Maltodextrin, Polyethylene glycol, Aspartame, Mannitol, Citric acid were purchased from S.D. Fine chemicals, Mumbai .Amaranth purchased from oxford laboratory, Mumbai.

Methods

Preformulation Studies:

It is defined as the determination of physical, chemical and mechanical properties of a new drug substance alone and when combined with excipients **[4]**. The overall objective of preformulation studies is to generate information useful in developing stable, safe and effective dosage form**.**

Solubility:

The maximum equilibrium amount of solute that can dissolve per amount of solvent is the solubility of that solute in that solvent under the specified conditions. Solubility is one of the characteristic properties of a substance and is used to describe the substance, to indicate a substance's polarity and to help to distinguish it from other substances.

Melting Point:

The melting point of a substance is the temperature at which the material changes from a solid to a liquid state. Pure crystalline substances have a clear, sharply defined melting point.The melting point was determined by using Capillary tube method.

Formulation and Development Mouth Dissolving Films:

Table-1: Composition of Formulations

Formulation Code & Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
BENAZEPRIL (mg)	20	20	20	20	20	20	20	20	20
HPMC E5 (mg)	200	250	300	-	-	-	-	-	-
HPMC E 3LV	-	-	-	200	250	300	-	-	-
HPMC 5 CPS	-	-	-	150	175	200	200	210	220
Maltodextrin (mg)	100	110	120	125	130	140	140	150	150
Propylene glycol	50	50	60	60	70	70	80	80	80
Aspartame (mg)	20	20	20	20	20	20	20	20	20
Citric acid (mg)	10	10	10	10	10	10	10	10	10
Water(ml)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Vanilla	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Amaranth	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Procedure:

Fast-dissolving films of Benazepril were prepared by the solvent-casting method.

The water-soluble polymers were soaked in half quantity of distilled water for overnight to obtain a uniform dispersion. Aqueous solution I was prepared by adding plasticizer to above polymeric solution and could stir for 4 hours and kept for 1 hour to remove all the air bubbles entrapped. Aqueous solution II was prepared by dissolving the Benazepril, mannitol, aspartame in specific proportion in remaining amount of distilled water.

Both aqueous solutions I and II were mixed and stirred for 1 hour and kept for 30min for sonication. Then the mixture solution was casted onto a plastic Petri dish having surface area of 63.64cm^2 and it was dried in the oven at 50^{0}C for 24 hour. The film was carefully removed from the Petri dish, checked for any imperfections, and cut according to the size required for testing(2×2cm^2).

Evaluation Parameters:

Appearance

All prepared films were checked for their appearances either they are transparent or opaque or presence of air bubble.

Thickness uniformity:

The thickness of the patch was measured using digital Vernier Calliper with a least count of 0.01 mm. The thickness was measured at different strategic points of the film and average was taken and SD was calculated **[6]**.

Weight uniformity:

Weight variation is studied by individually weighing randomly selected films and calculating the average weight. And standard deviation was calculated **[7]**.

Drug Content uniformity:

Drug content determination of the film was carried out by dissolving the films of required size in pH 1.2 phosphate buffer (0.1N HCl) using magnetic stirrer for 1hour. The drug concentration was then evaluated spectrophotometric ally at 254 λmax of nm. The determination was carried out five times for all the formulations and average with standard deviation was recorded **[8]**.

Folding endurance:

Folding endurance was determined by repeated folding of the film at the same place till the strip breaks. The number of times the film is folded without breaking was computed as the folding endurance value **[9]**.

Surface pH of film:

The pH was determined by dissolving a film in 2 ml of pH 1.2 phosphate buffers and then the pH of the obtained solution was measured by pH meter. The average of five determinations for each form **[10].**

In vitro Disintegration Time

The film size required for dose delivery (4 cm^2) was placed on a glass Petri dish containing 10 ml of pH 1.2 phosphate buffer (0.1N HCl). The time required for the film to break was noted as in vitro disintegration time **[11, 12, and 13]**.

In vitro drug release studies

900 ml of 0.1N HCl was placed in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium could equilibrate to temperature of $37^0C \pm 0.5^0C$. A Film was placed in the vessel and was covered; the apparatus was operated up to 1 h at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions. Suitable dilutions were done with dissolution medium and were analyzed spectrophotometrically at λmax of 254 nm using a UV-spectrophotometer **[14, 15]**.

Data analysis:

Kinetic Data / Model fitting

Drug release mechanisms and kinetics are two characteristics of the dosage forms which play an important role in describing the drug dissolution profile from a dosage forms. The dissolution data obtained is fitted to mathematical models and the best fit is obtained to describe the release mechanism of the drug [16, 17]. A number of mathematical models have been developed to describe the drug dissolution kinetics from drug delivery system e.g., Higuchi (cumulative % drug release versus square root of time); First order (log cumulative % drug remaining versus time), Zero order (cumulative % drug release versus time) and Korsmeyer Peppas model (log cumulative % drug release versus log time)[18].

Compatibility studies (Fourier Transform Infrared Spectroscopic studies):

The drug-excipient interaction study was carried out using by KBr pellet method. To study the compatibility of various formulation excipients with drug, solid admixtures were prepared by mixing the drug with formulation excipient separately and it was filled and characterized by using Fourier transform infrared spectroscopy (FTIR)**[19,20]**.

RESULTS AND DISCUSSION:

Preformulation Studies:

Solubility studies:

Solubility study for Benazepril was carried out at room temperature. The drug solubility in water was found to be 67 µg/ml while the standards show that benazepril is soluble to an extent of 69 µg/ml. It is a good solubility in the chosen vehicle ensuring the movement of the drug through delivery system.

Melting Point: Melting point of Benazepril was determined by capillary method and found to be 148°C which correlates with that of standard melting point value of Benazepril indicating its purity.

Table2: Melting Point of a Drug

Trails	Melting point()		
	Observed value	Average value	Reference value
1	147	147	146-149
2	146		
3	148		

Formulation and development of fast dissolving oral films:

Fastdissolving oral films of Benazepril were prepared by solvent-casting technique using combination of HPMC E5, HPMC E3LV, HPMC 5CPS, Maltodextrin, and Polyethylene Glycol in different ratios.

Physical characterization of FDOFs was carried out by visual inspection and the following was observed.

1. The films were evenly coloured and no migration of color was observed.
2. F1 to F3, films with more HPMC were found to be thick and brittle.
3. F4 to F6 was found to have more tackiness which indicates that the physical handling of these films is difficult.
4. Increased opacity and decreased transparency is due to increase in the amount of maltodextrin proportionately to HPMC. Slightly opaque and opaque formulations were found to be F6 and F7.
5. The films obtained from all the formulations had smooth surface on either side.
6. F7 to F9 films was found to be good film property and with non-tacky and easy to peel nature.

Table 3: Preliminary Characteristics of Formulations F1-F9

Code and properties	Film property	Tacky property	Ease of handling
F1	Poor	Non-tacky	Thick & brittle
F2	Poor	Non-tacky	Slightly thick & brittle
F3	Poor	Non-tacky	Slightly thick & brittle
F4	Poor	Non-tacky	Thin, brittle, difficult to peel
F5	Average	Non-tacky	Thick, easy to peel
F6	Average	Non-tacky	Brittle, opaque
F7	Average	Non-tacky	Opaque, easy to peel
F8	Excellent	Tacky	Thin, easy to peel
F9	Good	Non-tacky	Easy to Peel

Fig.1: Picture of FDFs prepared by using Different polymers

Evaluation of films:

Table 4: Evaluation Parameters of films F1-F9

CODE	Thickness (µm)	Weight variation (mg)	Folding Endurance (Count)	Surface pH	Content uniformity/ Assay (%)	In vitro Disintegration Time (sec)
F1	74±2	57.14±0.6	58±2	6.55±0.03	98.8±0.2	25±2
F2	75±1	52.22±0.1	54±2	6.74±0.01	92.44±0.46	24±2
F3	80±3	58.4±0.1	62±1	6.54±0.011	89.65±0.14	30±2
F4	82±2	60.2±0.1	64±4	6.6±0.02	95.5±0.21	22±2
F5	80±1	71.5±0.5	86±3	6.89±0.010	97.32±0.3	20±2
F6	88±1	62.55±0.1	70±1	6.88±0.01	98.7±0.8	18±2
F7	86±2	70.5±0.3	95±4	6.93±0.02	86.7±2.2	14±2
F8	83±6	66.65±0.3	106±4	6.93±0.11	99.7±0.5	10±3
F9	87±1	71.3±0.1	96±1	6.94±0.01	98.6±0.45	14±2

In vitro drug release: Being the fast disintegrating formulations the release rates of all the formulations were very rapid. It was noticed that the films got hydrated rapidly and began to dissolute the drug within minutes. This may be due to the water solubility of the drug and the polymer. The water-soluble filler mannitol was reported to be used as inert carrier to form a high water soluble dispersion with active agents. Films formed by higher quantity of polymer had shown slower dissolution rate this might be due to the increase level of polymer, results in formation of high viscosity gel layer caused by more intimate contact between the particles of polymer results in decreased in mobility of drug particles in swollen matrices, which leads to decrease in release rate. From the In vitro drug release, it was observed that in formulation containing multiple polymers shows best results. It was found that addition of maltodextrin resulted in faster drug release from the films.

Table 5: *In vitro* drug release Studies of Formulation F-1 to F-9

Time (min)	Formulation code								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	23.99±0.35	40.12±0.35	27.64±0.21	36.78±0.58	16.8±0.26	21.67±0.15	36.86±0.39	49.12±0.49	47.09±0.25
2	35.41±0.23	54.99±0.12	37.16±0.65	47.09±0.24	24.99±0.35	34.97±0.19	46.79±0.45	69.89±0.41	68.18±0.53
3	47.09±0.46	66.14±0.45	47.89±0.21	55.89±0.41	37.16±0.65	44.81±0.35	56.87±0.32	87.56±0.54	85.72±0.34
4	55.64±0.41	75.74±0.49	56.89±0.21	66.18±0.55	47.09±0.21	54.97±0.31	65.61±0.41	93.45±0.23	91.45±0.28
5	63.92±0.04	84.65±0.34	66.18±0.65	76.92±0.43	56.89±0.21	63.51±0.42	74.95±0.37	96.78±0.48	94.51±0.35
6	74.64±0.19	91.18±0.23	76.92±0.24	84.69±0.21	66.18±0.65	72.65±0.37	83.12±0.41	97.45±0.42	96.99±0.23
7	82.43±0.43	94.89±0.31	85.72±0.78	92.19±0.55	76.92±0.24	81.82±0.41	89.82±0.21	98.01±0.51	95.99±0.26
8	89.88±0.55	96.08±0.56	91.45±0.32	93.46±0.43	85.72±0.78	87.19±0.11	91.43±0.43	98.39±0.67	96.80±0.38
9	91.23±0.54	97.61±0.67	93.04±0.76	95.25±0.41	90.14±0.54	89.13±0.13	92.30±0.32	99.49±0.36	97.22±0.25
10	93.24±0.53	98.19±0.54	94.51±0.43	97.84±0.21	91.45±0.32	91.41±0.12	93.21±0.24		98.88±0.94
11	94.45±0.32	99.33±0.11	95.82±0.54	99.13±0.41	93.04±0.76	92.51±0.14	94.82±0.41		
12	95.52±0.43		96.99±0.65		94.51±0.43	93.52±0.41	96.99±0.26		
13	96.04±0.58		98.89±0.32		95.82±0.54	95.89±0.26	99.29±0.25		
14	99.16±0.43				96.99±0.65	96.90±0.18			
15					97.04±0.58	98.86±0.05			
16.					98.28±0.26				

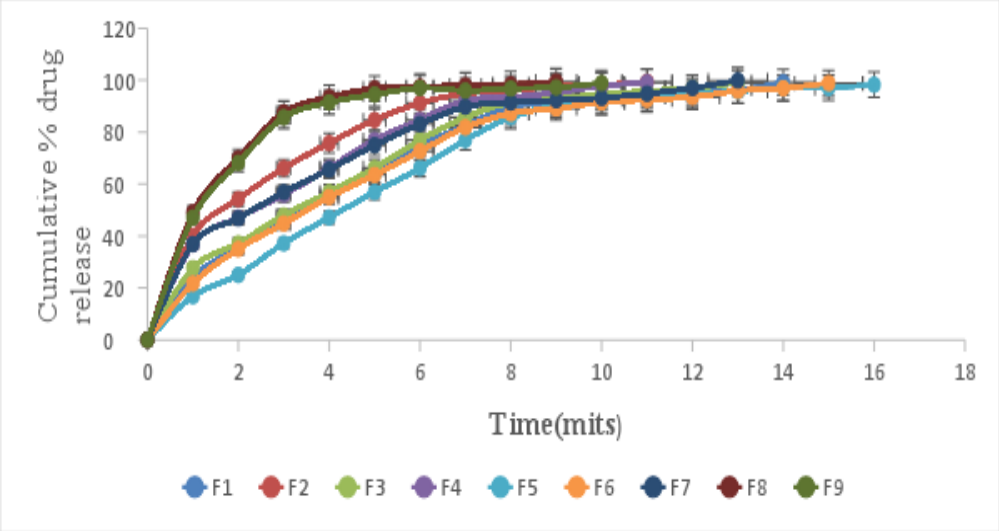

Fig. 2: Cumulative % drug release of formulation of F1-F9

Data analysis: Kinetic Data / Model fitting

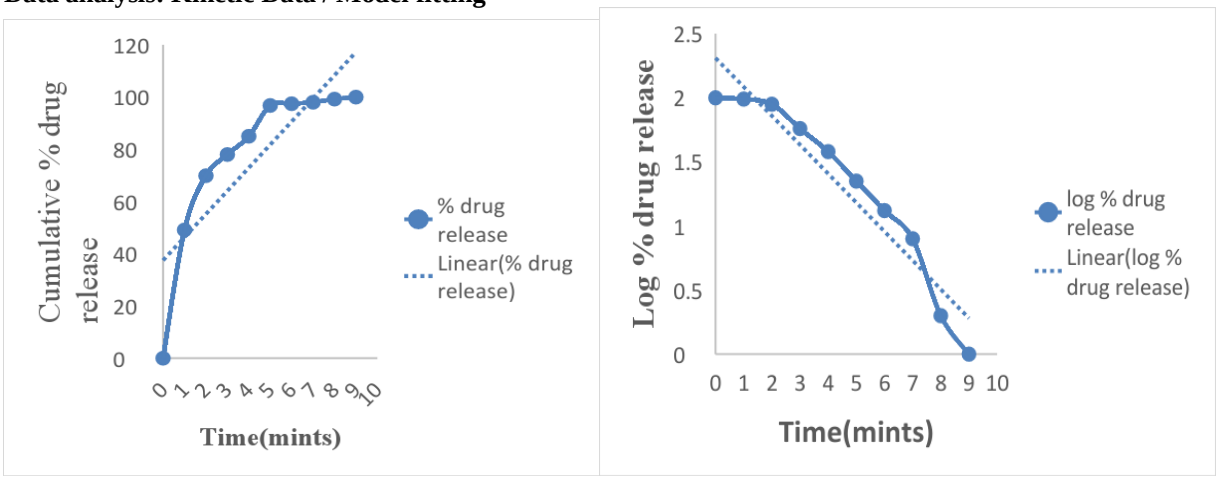

Fig. 3: Zero order kinetic plot, first order kinetic plot of optimized formulation (F8)

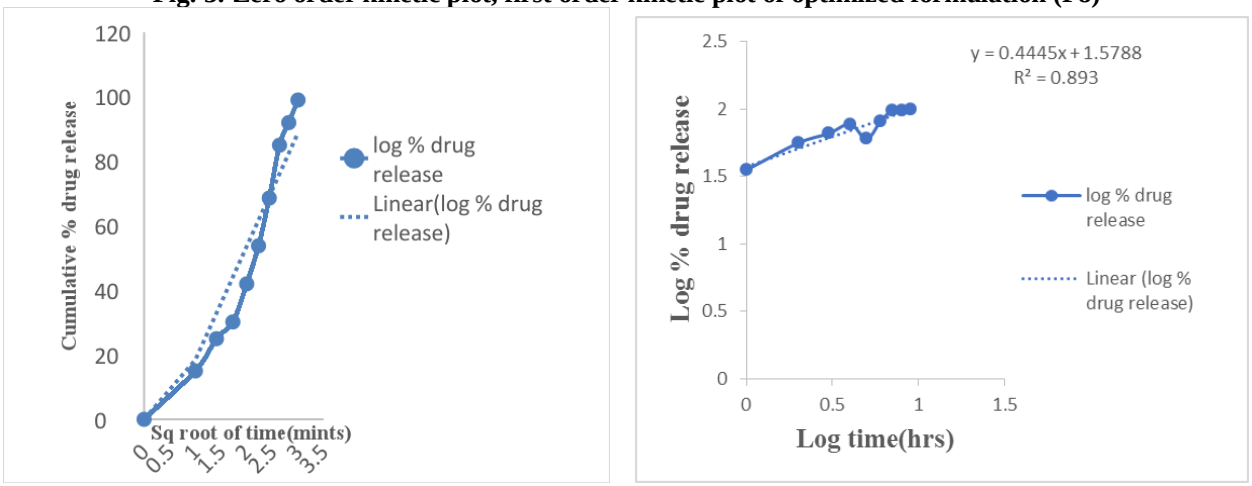

Fig. 4: Higuchi kinetic plot, Korsmeyer–Peppas kinetic plot of optimized formulation (F8)

FT-IR Studies:

FTIR studies were carried out on drug and drug-excipient samples. In FTIR spectra of the pure drug the observed peaks at 2989.97 cm^{-1} due to C-H stretching, 1590.50 cm^{-1} due to C=C aromatic stretching, 3195.78 cm^{-1} due to N-H stretching, 1377.73 cm^{-1} due to C-O stretching were in the range of reference peaks. It ensures its purity.

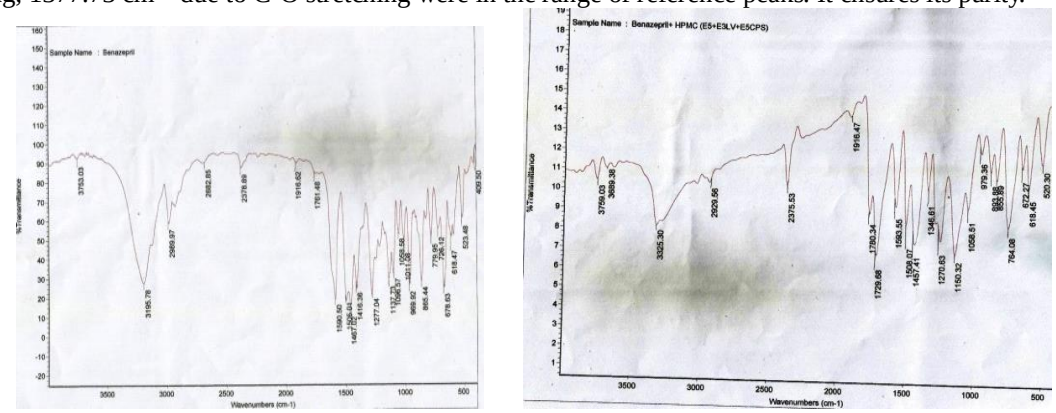

Fig. 5.FT-IR Spectra of Benazepril, Benazepril with HPMC mixture (1:1)

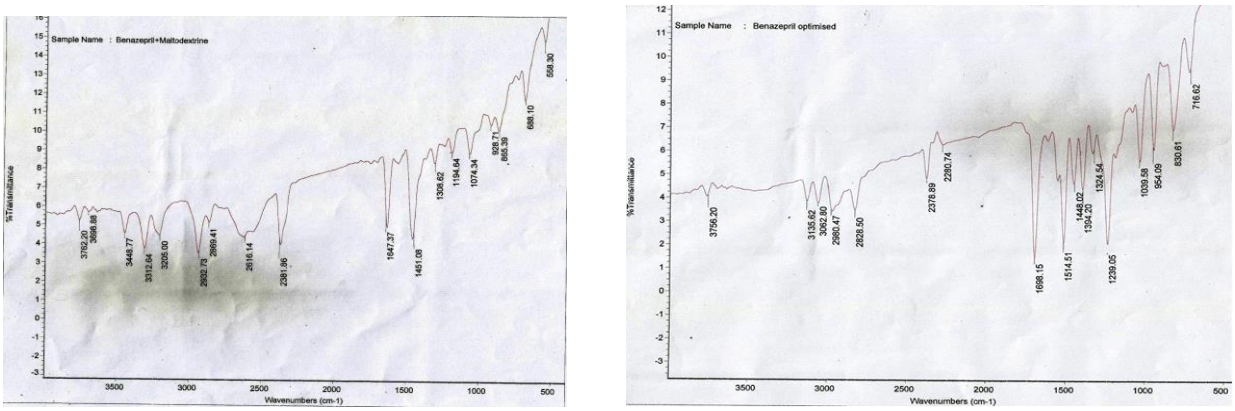

Fig. 6: FT-IR Spectra of Benazepril with maltodextrin (1:1), FT-IR Spectra of optimized formulation

CONCULSION:

In present work attempt was made to formulate and evaluate fast dissolving drug delivery system. Attempts were made to achieve rapid drug dissolution from the dosage form. However, with our greater understanding of the structure and function of the oral mucosa, and fast dissolving drug delivery system, more and more new drug products are being developed for fast dissolving drug delivery. The properties of the drug, the characteristics of the oral dissolving device, selection of in-vitro model are all important for safe and effective drug delivery.

In the Preformulation studies, determination of melting point and determination of solubility was carried out and the values obtained were within the range. And FTIR studies results revealed that there was no incompatibility between drug and excipients.

Thus, fast dissolving films were formulated by varying proportions of polymers by solvent casting method and they were evaluated. The physical appearance of the film formulations was transparent in nature. The drug content of the formulations was in the range of 86.7±2.2 to 99.7±0.5, low SD values were showing content uniformity. The pH of the formulations was in the range of 6.54±0.011 to 6.93±0.11, which lies in the normal pH range of the oral mucosa and would not produce any irritation to the mucosa.

The thickness uniformity of the film formulations generally assures its dose accuracy per strip. It was observed that as the polymer concentration increased thickness was also increased. Low standard values assured that films were uniform in thickness. Thickness of films was in the range of 74±2 to 83±6.

From the In vitro disintegration data it was observed that, the disintegration time of films containing combination of HPMC Grades was more when compared with films containing individual HPMC. And in case of films containing maltodextrin, increased amount of maltodextrin resulted in rapid disintegration of films.

In vitro drug release studies were carried out to select appropriate polymer composition for the formulation having suitable drug dissolution property for the dosage form. Maximum drug was released from the formulation F8 within 9 minutes. Based on the physico-mechanical properties and in-vitro drug release, the formulation F-8 was concluded as the Optimized formulation.

In the present work, it can be concluded that the fast dissolving film formulation can be an innovative and promising approach for the delivery of Benazepril for the treatment of Hypertension.

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