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FORMULATION AND EVALUATION OF CARVEDILOL SUBLINGUAL TABLET

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Abstract:

Carvedilol is an oral antihypertensive agent. Due to its poor water solubility it posses problems of variable bioavailability and bioequivalence. In the present work an attempt was done to develop sublingual tablets of carvedilol using different superdisintegrants like crosscarmellose sodium, crosspovidone and sodium starch glycolate in different ratios. As carvedilol is a poor soluble drug the solubility was enhanced by solid dispersion method. Tablets were prepared by direct compression technique. Prepared tablets were evaluated for thickness, uniformity of weight, hardness, friability, wetting time, in-vitro disintegration time, drug content and in vitro drug release. All the formulations were evaluated for the characteristics of sublingual tablets mainly in terms of .disintegration time and dissolution studies .Out of the 7 formulation, formulation F7 shows the maximum drug release. The formulation F7 consist of super disintegrant crosscarmellose sodium 5% and drug polymer in the ratio 1:4.From the literature it was evident that drug release was increased with increase in concentration of the polymer. So the formulation F7 was optimized as the best formulation.

Keywords: *Carvedilol, Sublingual tablet, Super disintegrants, Bioavailability*

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INTRODUCTION:

Drug delivery via sublingual mucous membrane is considered to be a promising alternative to the oral route. This route is useful when rapid onset of action is desired. In terms of permeability, the sublingual area of the oral cavity is more permeable than cheek and palatal areas of mouth. The drug absorbed via sublingual blood vessels bypasses the hepatic first-pass metabolic processes giving acceptable bioavailability with low doses and hence decreases the side effects. Sublingual drug delivery system is convenient for paediatric, geriatric, and psychiatric patients with dysphagia. .

In the present study, sublingual tablet of Carvedilol was attempted with the aim to develop a dosage form that was easy to administer, provide faster onset of action and also enhanced bioavailability of the drug. Carvedilol has been used in the management of hypertension. The drug is well absorbed from the gastrointestinal tract but its bioavailability is low (25%) due to extensive first pass metabolism. The physicochemical properties of carvedilol, its suitable half-life (6-10 h) and low molecular weight make it a suitable candidate for the formulation of sublingual tablet. The solubility of the drug has been enhanced by solid dispersion technique.

MATERIALS AND METHOD:

MATERIALS

Carvedilol was obtained from Balaji chemicals, Gujarat, superdisintegrants were obtained from Sanca pharma Kozhuvanal, talc magnesium stearate were obtained from Otto chemie pvt limited.

METHODS

Preparation of solid dispersions

Carvedilol and polymer carriers like HPMC, PVP, β-CD and PEG4000 were taken in different ratio (1:1, 1:2 and 1:4). The carriers were dissolved in an adequate amount of methanol. The solvent was then rapidly evaporated with the aid of mild heat with constant vigorous stirring to form a uniform solid mass. The co-precipitate was crushed and desiccated under vacuum for 24 h, sized into different sieve fractions and stored in desiccator, until further use [4-5]

Formulation of sublingual tablet

The sublingual tablets of carvedilol were prepared by direct compression method. The drug and excipients were passed through sieve no.80 to ensure better mixing. In the formulation, each super disintegrant was employed in different concentration. The composition of sublingual tablet of carvedilol was shown in the table no:1. Drug or equivalent solid dispersion was mixed with mannitol by geometrical dilution method. The blend obtained was mixed with MCC and sodium saccharin for 5 min. To the above powder blend super disintegrants were added and mixed. Magnesium stearate and talc was then added to the above blend and then again mixed for 5 min. Powder blend was then directly compressed using 10 station tablet compression machine.

Table 1: Composition of Carvedilol sublingual Tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7
Carvedilol	3.25	-	-	-	-	-	-
Solid dispersion equivalent to 3.25mg Carvedilol		6.57	10.54	16.75	6.5	10.02	17.1
Mannitol	50	48.25	45	42	48.25	45	41
Avicel pH101		30.93					
Avicel PH102	30		27.21	24	28	26.73	22
Cross povidone			3				
Cross carmellose sodium	2.5				3	4	5
Sodium starch glycolate				3			
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Sodium saccharin	9.25	9.25	9.25	9.25	9.25	9.25	9.25

Based on drug content SD equivalent to 3.25mg of Carvedilol is taken

Evaluation of Developed Carvedilol Sublingual Tablets

Pre-Compression Characteristics: [6-9]

Bulk Density

The term bulk density refers to a measure used to describe a packing of particles. It is (gm/ml) and was determined using a weighing balance and measuring cylinder. Initially the weights of the measuring cylinder were tarred. Then powders were poured into the measuring cylinder using a funnel and weighed (M). Then volume of the powder (Vb) was taken. Bulk densities of the granules were calculated using following formula [5].

Bulk density = Weight of powder/Bulk volume

Tapped Density

Blend was tapped for a fixed number of taps. The weight of the blend (M and the minimum volume (Vt) occupied in the cylinder were measured. The tapped density were calculated using following formula

Tapped density = Weight of powder / Tapped volume

Compressibility index

It is one of the most important parameter to characterize the nature of powders and granules. It can be calculated from the following equation.

Compressibility index = Tapped density - Bulk density / Tapped density X 100

Hausner Ratio

Hausner ratio (HR) is an indirect index of ease of powder flow. Lower the value of Hausner ratio better is the flow property.

Angle of Repose

Angle of repose was determined using funnel method. In this method the blend was poured through a funnel which can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and angle of repose was calculated using the formula,

$$\theta = \tan^{-1}(h / r)$$

Post-Compression Characteristics:

After compression of powder, the tablets were evaluated for color, odor, taste, diameter, thickness and physical characteristics like hardness, friability, drug content, content uniformity, disintegration time and in vitro drug release

Tablet Thickness

Tablet thickness of the tablets was determined using vernier calipers.

Weight Variation Test

IP procedure was followed. Twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight.

Hardness

The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness were measured in terms of kg/cm2. . Tablet was placed vertically between the jaws of the tester. The two jaws placed under tension by a spring and screw gauge. By turning the screw, the load was increased, and at collapse the applied pressure from the spring was measured.

Friability

These tests are intended to determine the physical strength of tablets and are applicable to compressed tablet. 10 tablets were weighed and placed in Roche friabilator and rotated 100 times at 25rpm. The tablets were weighted and percent friability was calculated by the following formula.

$$\%F = (Wo - W) / Wo \times 100$$

Where, F = friability

Wo = initial weight of the ten tablets

W = final weight of the ten tablets.

Drug Content estimation

Ten randomly selected tablets were weighed and powdered in a glass mortar. Weight equivalent to 3.25mg Carvedilol were weighed and dissolved in 10 ml of methanol in volumetric flask, the volume was made up to 100 ml with PBS of pH6.8 and the solution was filtered. An aliquot of 1 ml of solution was diluted to 10 ml with PBS of pH in separate volumetric flask. The content in the tablets were determined spectrophotometrically at 241 nm.

Wetting time

The tablets to be evaluated were placed at the centre of 2 layers of absorbent. After the paper was thoroughly wetted with distilled water, excess water was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded using a stopwatch [7].

***In vitro* disintegrating test**

Disintegration times for the sublingual tablets were determined using USP tablet disintegration apparatus. The medium used was phosphate buffer solution of pH 6.8. The volume of medium was 900 ml and temp was 37± 2 °C. The time taken (in secs) for complete disintegration of the tablets with no palatable mass remaining in the apparatus was measured.

***In-vitro* dissolution studies**

In-vitro dissolution studies of formulation were carried out using USP –typeII dissolution apparatus (paddle type) at 50 ± 1 rpm in 900 ml of PBS of pH 6.8 as dissolution media maintained at 37±0.50C. Aliquot of 10 ml was withdrawn at the specified time interval of 5, 10,15,20,25 and 30 minutes and were replenished with fresh dissolution medium. The samples were filtered, diluted and analyzed by UV-spectrophotometer at 241nm.

Stability study

Stability studies of tablets were carried out for as per ICH guidelines. Samples were stored at temperature of 25±2 0C/60 ± 5% RH for 6months and 40 ± 2oC/75 ± 5% RH for 1 month as given in Table no:12. Then the samples were analyzed for physical stability, dissolution time ,disintegration time and drug content.

RESULTS AND DISCUSSION:

Drug Polymer Interaction Studies:

All the reference IR peaks of the pure drug Carvedilol were also present in the spectra of mixture of drug- polymer and drug polymer -excipients. So FTIR study showed that there was no interaction between drug and polymer and excipients. So, the drug and polymer and excipients are compatible.

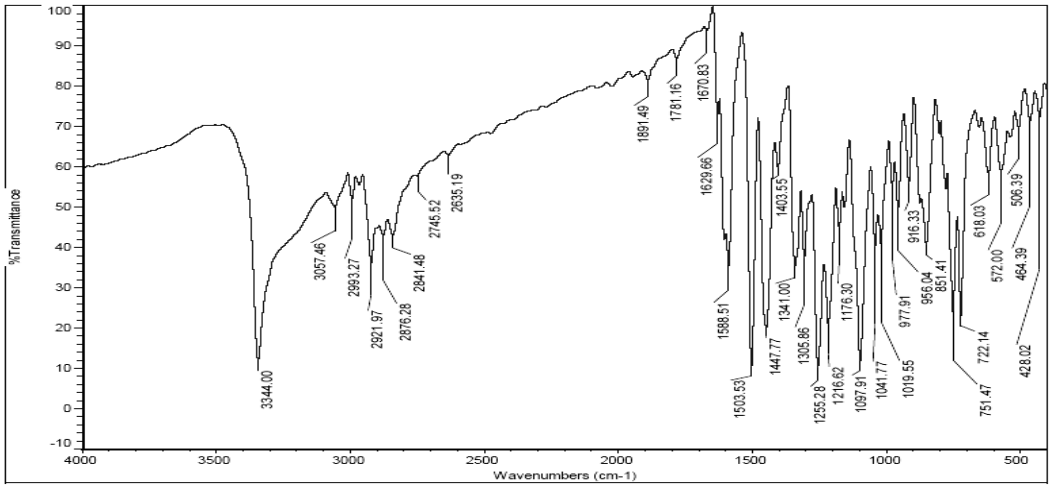


Fig.1: FT –IR spectrum of pure Carvedilol

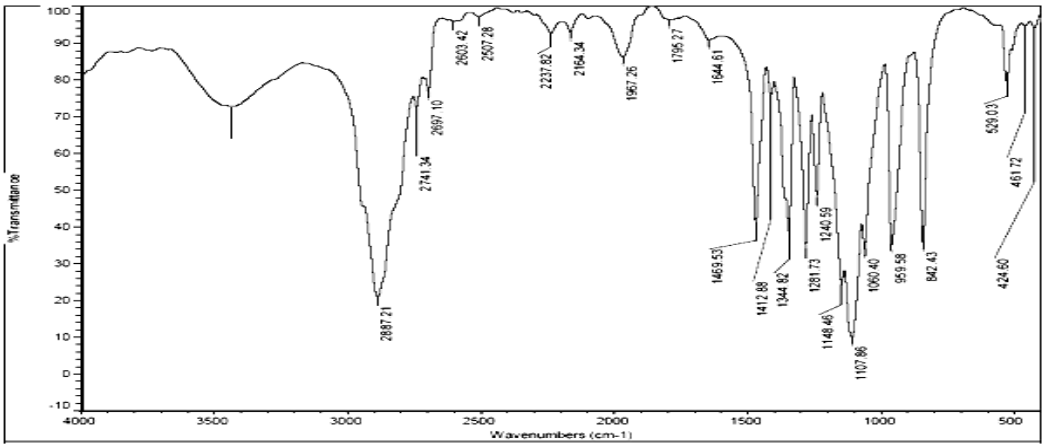


Fig.2: FT – IR spectrum of PEG 4000

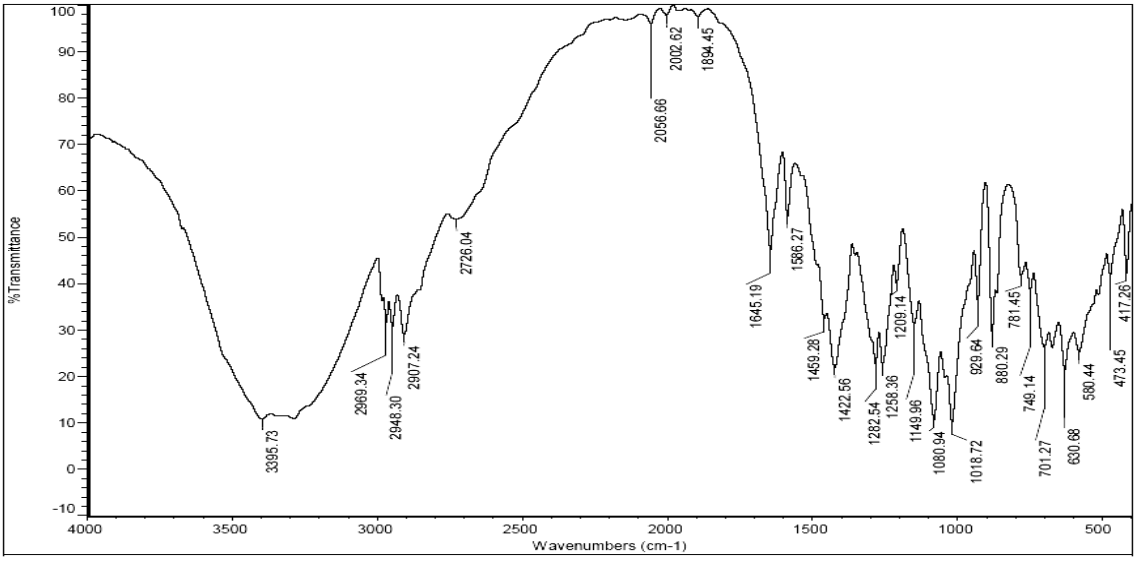


Fig.3: FT – IR spectrum of F7

The powder blend of all 7 formulations were subjected to pre-compression characteristics like bulk density, tapped density, hausners ratio and Carr's index, angle of repose and were given in Table.2

Table 2: Pre-compression characteristics of Carvedilol sublingual tablets

Formulation	Bulk density	Tapped density	Hausners ratio	Carrs Index	Angle of repose
F1	0.58±0.05	0.67±0.03	1.15±0.01	13.4	26.280
F2	0.75±0.07	0.99±0.04	1.32±0.03	24.2	33.070
F3	0.51±0.02	0.61±0.04	1.19±0.03	16.3	29.020
F4	0.54±0.01	0.60±0.03	1.11±0.02	10	25.400
F5	0.42±0.00	0.50±0.04	1.19±0.02	16	24.300
F6	0.49±0.01	0.58±0.02	1.18±0.01	15.5	27.140
F7	0.49±0.02	0.55±0.02	1.12±0.02	10	28.260

Weight variation

The weight variation of tablets was carried out by taking the average weight of 20 tablets. The weight of the tablet was 100mg; the acceptable weight variation range is 80mg to 250mg (± 7.5%) and the weight of the tablets are within the specified range.

Hardness

Hardness for tablets determines the resistance of the tablet to abrasion or breakage under conditions of storage, transportation and handling before usage. The hardness of the batch from F1-F7 were found to be mechanically stable and varying between 2.36-3 kg/ cm2.

Friability

Friability is needed for tablets to withstand force of compression applied during the manufacturing of tablets. The friability of all the formulated tablets were found to be between 0.41-0.74%.All the formulated tablets showed the percentage friability within the official limits (1%) except formulation F2.

Table 3: Post -compression characteristics of Carvedilol sublingual tablets

Formulation	Thickness (mm)	Weight variation (mg)	Friability %	Hardness Kg/cm^2
F1	2. 0±.070	100±1.00	0.55	2.36 ±0.05
F2	2.16±0.054	98±1.35	1.35	2.67 ±0.37
F3	2.2± 0.054	101±0.57	0.41	2.70 ±0.20
F4	2.2 ±0.054	99±.57	0.55	3.0±0.17
F5	2.14 ±0.054	101±1.43	0.73	2.8 ±0.20
F6	2.3 ±0.070	101±0.57	0.43	2.5 ±0.05
F7	2.22 ±0.044	101±1.00	0.59	2.4±0.11

Formulation	% Drug content	Wetting time (sec)	Disintegration time (sec)
F1	97.6 ±0.34%	99±2	97±1.5
F2	96.6 ± 0.32 %	240±2	205±3.6
F3	94.9±0.70%	72±2	50±2
F4	99.5±0.45%	67±3	48±1.5
F5	96.5±0.56%	63±2	40±1.7
F6	96.8 ±0.67%	55±3	33±1.5
F7	97.9±0.50%	50±1	28±3.6

Disintegration time (in secs) for all formulations were evaluated .F1 which consist of the drug alone with superdisintegrant cross carmellose (2.5%) disintegrate within 97sec.So formulations F2-F7 were prepared using solid dispersions instead of pure drug with varying concentration of superdisintegrants.Formulation F6 and F7; croscarmellose sodium was used in 4% and 5% concentration as superdisintegrants . The DT was found to be 33 and 28 secs respectively. This indicates that an increase in concentration of superdisintegrants decreased the DT. Finally it was concluded that formulation containing croscarmellose sodium (5%) was found to be best when DT was considered.

Wetting time

Wetting time for all the formulations were evaluated. The results to those for DT were found to be significant for wetting time. Formulation containing Avicel PH 102 as diluent and croscarmellose sodium as superdisintegrant (5%) exhibited low wetting time.

***Invitro* dissolution studies**

Invitro dissolution studies for all the formulations were done using PBS of pH 6.8 min and the cumulative percentage of drug released as a function of time for all formulations were tabulated in table no :5 and also represented graphically.

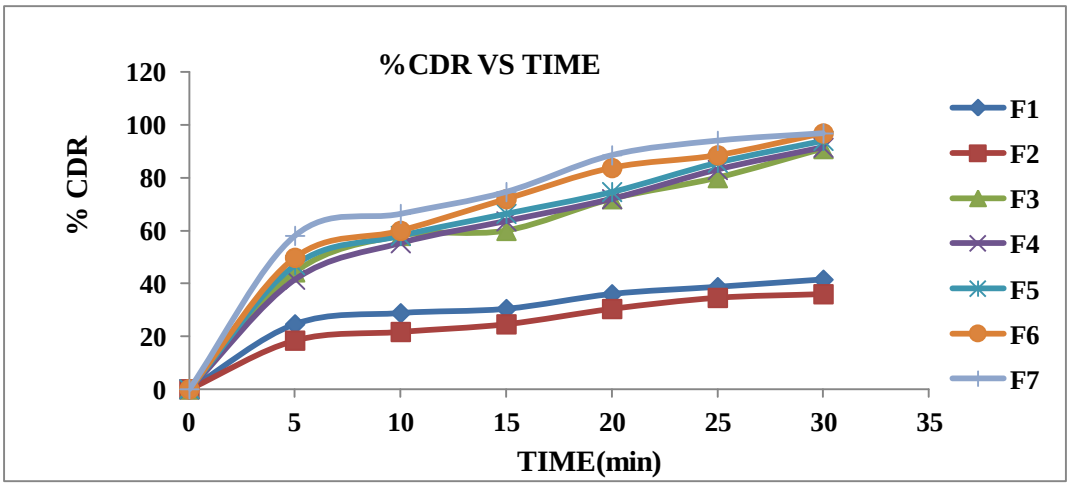
This study revealed that out of the 3 different superdisintegrants used the drug release was observed in increasing order as follows:

Crosspovidone < sodium starch glycolate < croscarmellose sodium

The formulation F7 consist of superdisintegrants crosscarmellose sodium 5% and drug polymer in the ratio 1:4.From the literature it was evident that drug release was increased with increase in concentration of the polymer. So the formulation F7 is optimized as the best formulation.

Table 4: Drug Release Profile of Carvedilol sublingual tablets

Time	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
5	24.60	18.42	44.30	41.50	47.00	49.80	58.10
10	28.80	21.70	58.10	55.30	58.10	60.00	66.40
15	30.40	24.60	60.00	63.60	66.46	72.00	74.70
20	36.00	30.40	72.00	72.00	74.70	83.80	88.60
25	38.70	34.60	80.00	83.07	85.80	88.60	94.10
30	41.50	36.00	91.00	91.50	94.10	96.90	99.80



Stability studies

The optimized tablets from batch F7 were charged for stability studies. There was no change in physical appearance, color. Formulations were analyzed at the end of 1months for the assay and dissolution studies and were tabulated in table no .6. In vitro dissolution profile showed that there were no significant changes in the release rate of the drug from optimized tablets at the end of 1 month.

Table 5: Stability studies of sublingual tablet

Formulation	%Drug content		%Drug release		Disintegration time (secs)	
	Before charging	After charging	Before charging	After charging	Before charging	After charging
F7	97.9	96.3	99.8	98.6	28	26

CONCLUSION:

Based on invitro dissolution studies it can be concluded that solid dispersion of carvedilol using cross carmellose sodium can improve the dissolution rate of carvedilol.The stability studies were performed on F7 batch as per ICH guidelines, which showed absence of any significant changes in drug content, drug release and disintegration time. Hence it can be concluded that formulating sublingual tablet of carvedilol using its solid dispersion can act as a promising tool for drug delivery. Further clinical studies are to be conducted to establish safely and to explore potentials of this dosage form to improve bioavailability, reduce the dose and to minimize the associated side effects of conventional drug delivery of Carvedilol.

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