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Research Article

FORMULATION AND EVALUATION OF MUCOADHESIVE TABLETS OF CARVEDILOL USING NATURAL BINDERS

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ABSTRACT

Carvedilol is a nonselective β-adrenergic blocking agent with α1-blocking activity which is used in the management of hypertension and angina pectoris and as an adjunct to standard therapy in symptomatic heart failure. Aim of the present work is to formulate and evaluate mucoadhesive tablets of Carvedilol using natural binders such as Chitosan and Guar Gum to reduce the first pass metabolism and frequency of administration. Cross Carmellose Sodium was used as superdisintegrating agent and Carbopol 940P was used as polymer. The tablets were formulated by direct compression method and were then evaluated for various pre-compression and post compression parameters such as hardness, friability, thickness, weight uniformity, drug content, drug release, swelling study, in-vitro drug release and in-vitro mucoadhesive strength. FTIR showed no interaction between drug and polymers. The optimized formula consisted of Carvedilol (6.25mg), Carbopol 940P and Chitosan in the ratio of 3:1, showed a maximum drug release after 7hrs, maximum swelling was attained in 6hrs and the highest mucoadhesive strength was 0.95N. Results indicate that release from optimized formulation of mucoadhesive buccal tablets of Carvedilol fits zero order kinetics and can by-pass the first pass metabolism and enhance the release of drug for extended period of time.

Keywords: Carvedilol, Mucoadhesive Buccal Tablets, Guar Gum, Chitosan, Mucoadhesive Strength.

1. INTRODUCTION

The primary aim of oral controlled drug delivery is to deliver drugs for longer period of time to achieve better bioavailability, which should be predictable and reproducible. But it's difficult due to the number of physiological problems such as fluctuation in the gastric emptying process, narrow absorption window and stability problem in the intestine[1]. To overcome these problems, different approaches have been proposed to retain dosage form in stomach. These include mucoadhesive or bioadhesive systems[2], swelling and expanding systems[3, 4], floating systems[5, 6] and other delayed gastric emptying devices.

Mucoadhesion/bioadhesion is generally understood to define the ability of a biological or synthetic material to "stick" to a mucus membrane, resulting in adhesion of the material to the tissue for a protracted period of time. For a material to be bioadhesive, it must interact with the mucus, which is a highly hydrated, viscous anionic hydrogel layer protecting the mucosa.

The principle of mucoadhesive preparation offers a simple practical approach and it's particularly useful to prolong the retention time of a dosage form in the stomach, thereby improving the oral bioavailability of the drug. Most of the mucoadhesive materials are either synthetic or natural or hydrophilic or water insoluble polymers and are capable of forming numerous hydrogen bonds because of the presence of hydroxyl, carboxyl or sulphate functional groups.

Binders are agents employed to impart cohesiveness to the granules. This ensure the

tablet remain intact after compression. Different binding agents can be useful in achieving various tablet mechanical strength and drug release properties for different pharmaceutical purpose. Natural binders like different starch, gums, mucilages, dried fruits possesses binding capacity as well as some other properties like filler, disintegrant and natural polymers are safe and economical than polymers like PVP.

Carvedilol is a nonselective β-adrenergic blocking agent with α1-blocking activity, it has vasodilating activity at α1 receptors; at higher doses calcium channel blocking activity may contribute. Carvedilol is used in the management of hypertension and angina pectoris, and as adjunct to standard therapy in symptomatic heart failure. The absolute bioavailability is about 25% and elimination half-life is about 6hrs. This is because of undergoing of drug to first pass metabolism in liver and gut wall[7]. Buccal mucosa is an attractive route for systemic delivery of many drugs since it is relatively permeable with a rich blood supply[9]. The mucoadhesive buccal drug delivery system offers several advantages as compared to traditional methods of systemic drug administration[10].

2. MATERIALS AND METHODS

2.1 Materials

Carvedilol is obtained as a generous gift sample from Mylan Laboratories, Hyderabad. Carbopol 940P from Merck Specialties Pvt Ltd, Chitosan and Guar Gum from SEZ Fine Chemicals, India. All other reagents and chemicals used were of analytical reagent grade.

2.2 Preparation of MucoadhesiveTablets of Carvedilol

All the ingredients including drug, excipients and polymers were made accurately in different ratios according to the batch formula to select optimum formulation. The amount of drug was established according to its clinical use and doses usually contain in some brand drug products. Different components in each formula were mixed by triturating in glass motor and pestle for 30 minutes. The mixture was then compressed using 6mm flat-faced punch using single stroke punching machine. (See table no.1)

3. Evaluation Tests

3.1 Fourier Transform Infrared (FTIR) Analysis

IR study was carried out to check compatibility between Carvedilol and all other excipients. FTIR spectra of purified drug and excipients were recorded using an infrared spectrophotometer (Shimadzu-8400S). The base line correction was done using dried potassium bromide. Uniformly mixed sample of Carvedilol and potassium bromide were kept in a sample holder and a spectrum was recorded over the wave number 400-4000 cm^{-1}.

3.2 Angle of Repose

Angle of repose for blend of each formulation was determined by fixed funnel method. The funnel was kept at fixed height (h), above a plane of paper kept on a flat horizontal surface. Angle of repose was determined by following equation,(See table no.2)

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

Where,
θ =angle of repose,
h=height between the lower tip of the funnel and the base of the heap of the blend,
r= radius of the base of the heap formed.

3.3 Carr's Compressibility Index (CCI) and Hausner's Ratio (HR)

It is used to evaluate flow ability of powder by comparing the bulk density and tapped density of a powder. Bulk density and tapped density was determined using bulk density apparatus. (See table no.2)

$$CCI=\frac{(TD-BD)}{TD}\times 100$$

$$HR=\frac{TD}{BD}$$

Where, TD= tapped density,
BD= bulk density.

3.4 Hardness

The resistance of tablets to shipping or breaking under the condition of storage, transportation and handling before the use depends on its hardness. The tablets should be sufficiently hard to resist breaking during normal handling and wet soft enough to disintegrate properly after swallowing. The hardness of tablets measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm^2 (See table no.3)

3.5 Weight Uniformity, Thickness and Friability

Randomly selected 20 tablets from each batch were subjected to weight variation test as per Indian Pharmacopoeia 2007. Each tablet was weighed individually to calculate the average weight and the percent variation in each tablet was calculated (See table no.3).

3.6 Drug Content

Three tablets from each batch was taken in separate 100 ml volumetric flasks containing 100ml of phosphate buffer (pH-6.8) containing 20% methanol and were kept for 24 hours under constant stirring. The solutions were then filtered, diluted suitably and analyzed at 241 nm using UV-Spectrophotometer. The average of three tablets was taken as content of drug in one tablet unit (See table no.3)

3.7 In-vitro Dissolution Studies

The United State Pharmacopoeia (USP) type II dissolution apparatus was used to study the release of drug from buccal tablets. The dissolution medium consisted of 500ml of phosphate buffer (pH-6.8) containing 20% methanol. The release was performed at 37±0.5 ℃ , at a rotation speed of 50rpm. Samples (5ml, at each time) were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through Whatman filter paper no. 41 with appropriate dilutions with phosphate buffer(pH-6.8) and were assayed spectrophotometrically at 241nm against phosphate buffer as blank (See table no.6).

3.8 Swelling Study

Swelling study was performed on 1% agar gel plates. Twenty tablets were weighed and average weight of each four tablets was calculated. The tablets were placed on the gel surface in five petri dishes (each containing four tablets), which were placed in an incubator at 37℃. Four tablets were removed at the time intervals of 1, 2, 4 and 6hrs, excess water from the surface was removed carefully using filter paper and the swollen tablets were weighed. (See table no.5)

The swelling index was calculated by using formula,

Swelling Index = [(wet weight – dry weight)/wet weight] × 100.

3.9 In- Vitro Bioadhesive Strength:

The term bioadhesive implies attachment of a drug carrier system to a specific biological location. In-vitro bioadhesive strength of tablets was measured using modified physical balance. Porcine buccal mucosa was used as a model membrane and phosphate buffer pH 6.8 was used as moistening fluid. Bioadhesive studies were performed in triplicate and average strength was determined. From the Mucoadhesive strength, force of adhesion was calculated. (See table no.4)

Force of Adhesion (N) = (Bioadhesive strength/100) × 9.81

Table 1: Formulation

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Carvedilol (mg)	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Carbopol 940P (mg)	-	2.5	5	7.5	-	2.5	5	7.5
Chitosan (mg)	10	7.5	5	2.5	-	-	-	-
Guar Gum (mg)	-	-	-	-	10	7.5	5	2.5
Cross Carmellose Sodium (mg)	-	5	-	5	-	5	-	5
Lactose (mg)	80	75	80	75	80	75	80	75
Magnesium Stearate (%)	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75
Talc (%)	2	2	2	2	2	2	2	2
Total Weight (mg)	100	100	100	100	100	100	100	100

Table 2: Flowability Parameters of Physical Mixture of Carvedilol Buccal Tablets

Formulation Code	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (°)
F1	0.445	0.529	16.00	1.17	27.36
F2	0.448	0.530	15.60	1.18	27.12
F3	0.490	0.575	14.80	1.18	27.72
F4	0.470	0.550	14.60	1.17	26.72
F5	0.496	0.601	17.60	1.16	26.17
F6	0.456	0.539	15.40	1.18	27.91
F7	0.462	0.537	14.00	1.16	25.38
F8	0.458	0.580	16.20	1.17	26.52

Table 3: Evaluation of Prepared Mucoadhesive Buccal Tablets Of Carvedilol

Formulation Code	Weight Variation (mg)	Drug content (%)	Friability (%)	Hardness (kg/cm$^{2)}$	Thickness (mm)
F1	101.0	99.48	0.19	6.7	2.61
F2	101.38	99.46	0.21	6.8	2.60
F3	101.44	100.05	0.41	7.2	2.58
F4	101.21	100.12	0.13	7.6	2.58
F5	101.01	98.92	0.75	7.4	2.64
F6	101.18	94.12	0.54	6.1	2.44
F7	101.24	93.91	0.36	6.5	2.36
F8	101.36	97.61	0.48	6.8	2.12

Table 4: In-vitro Mucoadhesive strength

Batch Code	Mucoadhesive Strength (gm)	Force Of Adhesion (N)
F1	8.5	0.83
F2	8.2	0.80
F3	9.2	0.90
F4	9.7	0.95
F5	7.8	0.76
F6	8.0	0.78
F7	8.4	0.82
F8	9.5	0.93

Table 5: In-vitro Swelling Study

Formulation Code	1 (hr)	2 (hr)	4 (hr)	6 (hr)
F1	30.76	39.23	Tablet Breaks	-
F2	25.00	33.42	42.31	44.23
F3	35.96	42.11	54.39	58.33
F4	27.64	43.49	54.14	62.11
F5	41.66	50.71	53.17	54.23
F6	28.63	46.92	55.32	60.21
F7	32.54	42.69	51.38	56.26
F8	26.17	34.82	40.55	49.83

Table 6: Cumulative % drug release

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
15	23.45	24.56	26.54	26.66	33.72	26.14	23.12	25.97
60	44.51	33.82	42.51	57.14	62.19	58.32	55.44	59.34
120	56.83	55.72	52.86	68.21	66.78	67.54	66.14	68.78
180	63.91	72.84	65.21	80.74	79.21	73.44	79.56	74.22
240	77.73	83.21	73.02	88.12	87.45	81.24	87.45	82.24
300	88.26	87.41	87.10	92.45	90.98	89.36	91.12	88.56
360	93.54	92.34	90.21	95.87	92.54	92.21	93.87	92.21
420	96.22	94.89	93.45	98.86	95.67	94.65	95.54	95.87

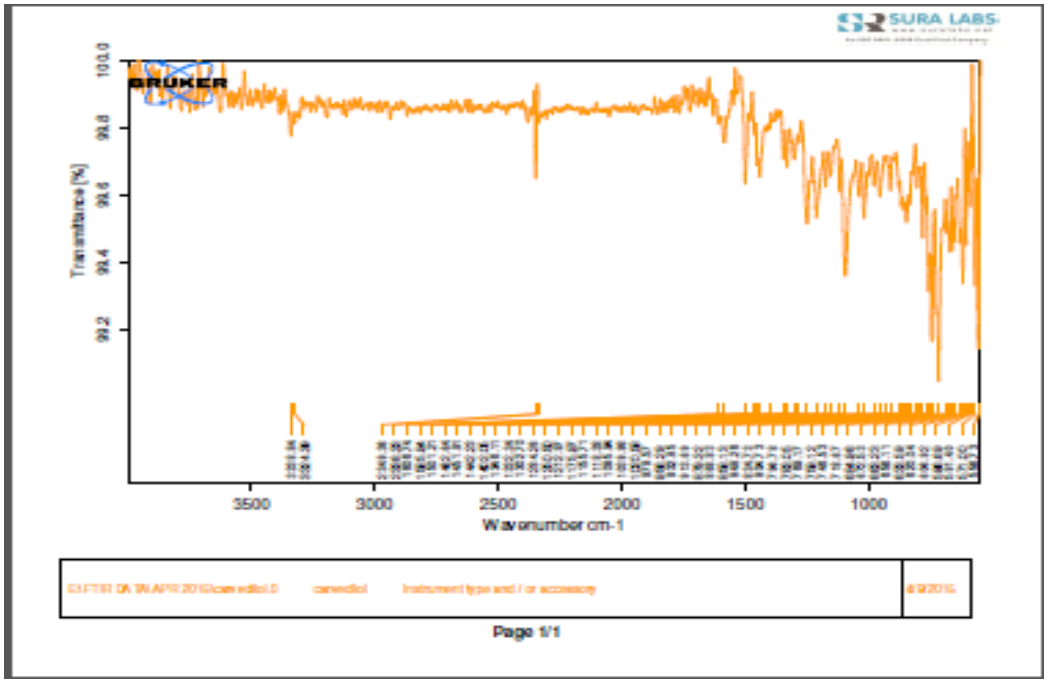

Fig. 1: I.R Spectra of Carvedilol

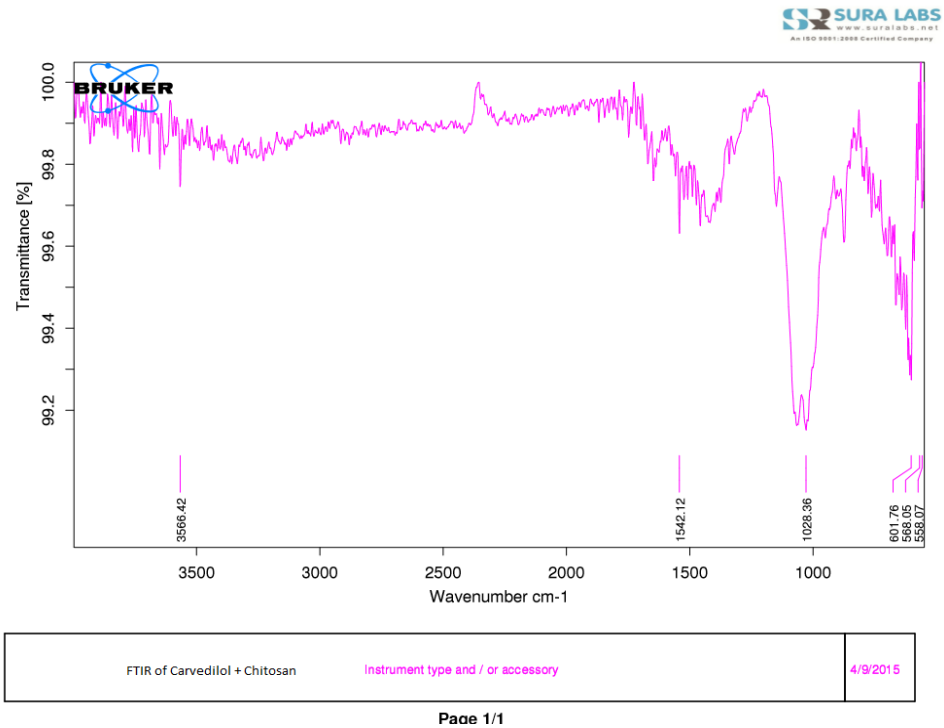

Fig. 2: I.R Spectra of Carvedilol and Chitosan

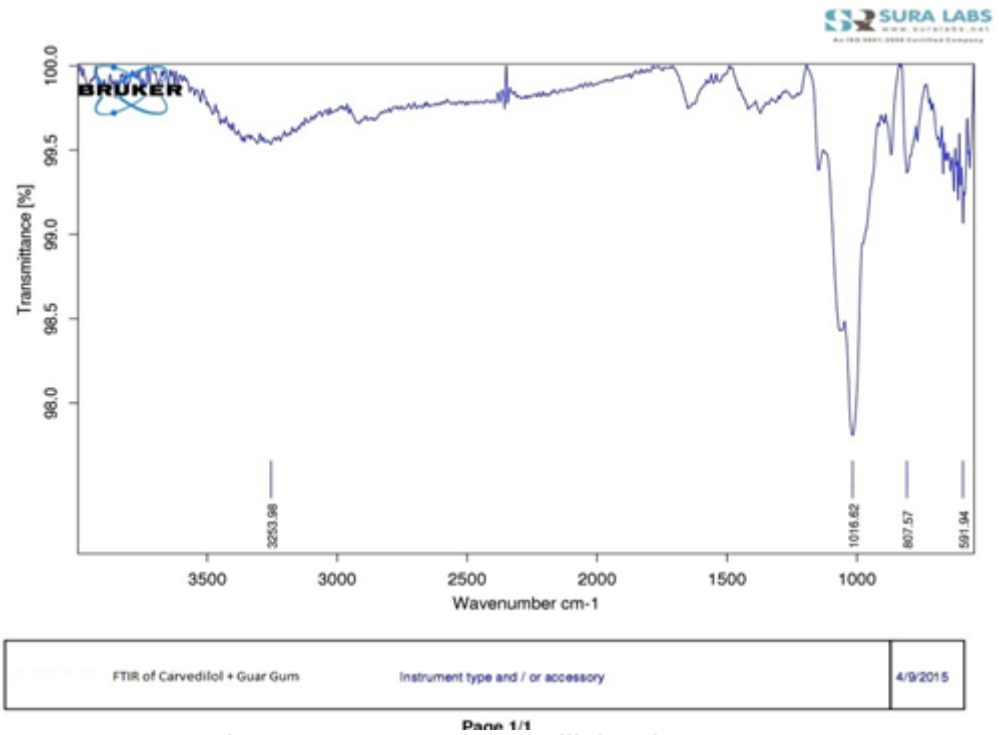

Fig. 3: I.R Spectra of Carvedilol and Guar Gum

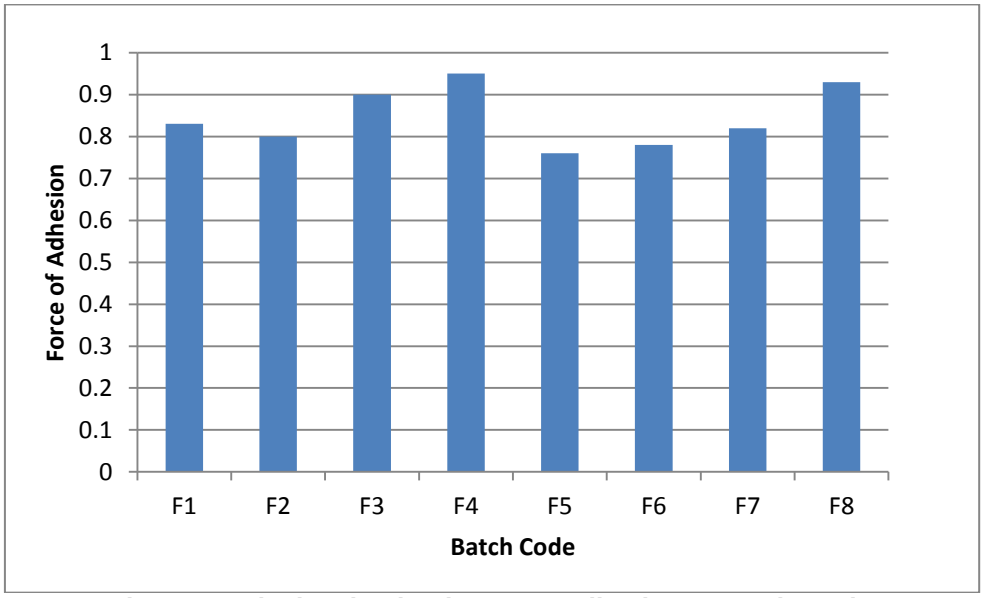

Fig. 4: Graph showing in-vitro Mucoadhesive strength study

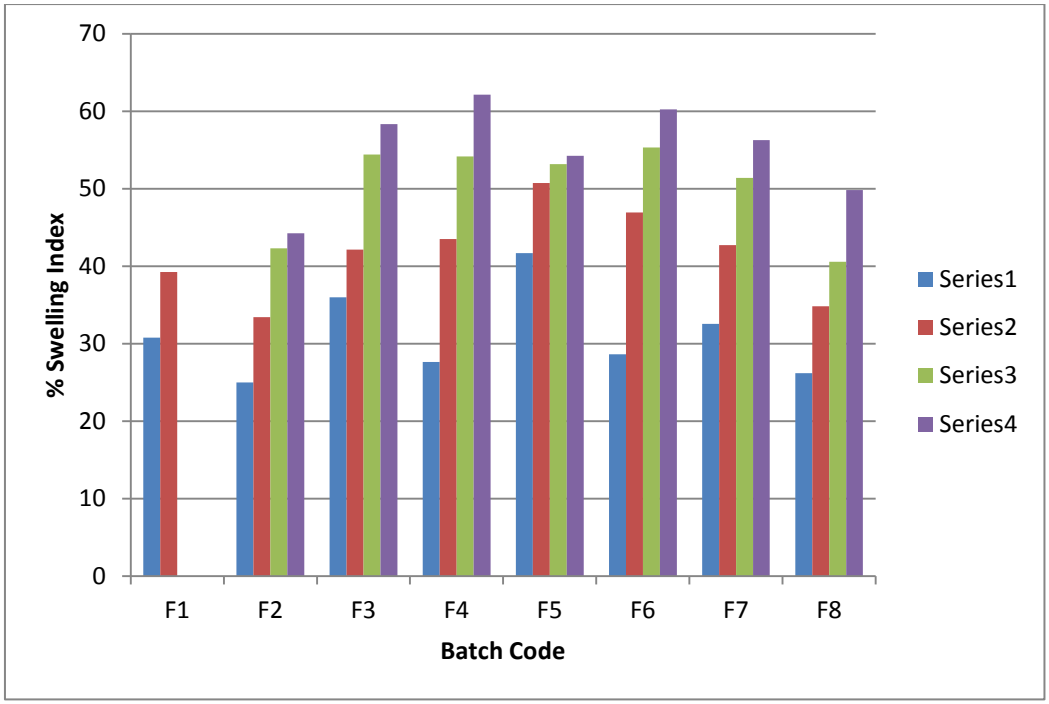

Fig. 5: Graph Showing In-vitro swelling study

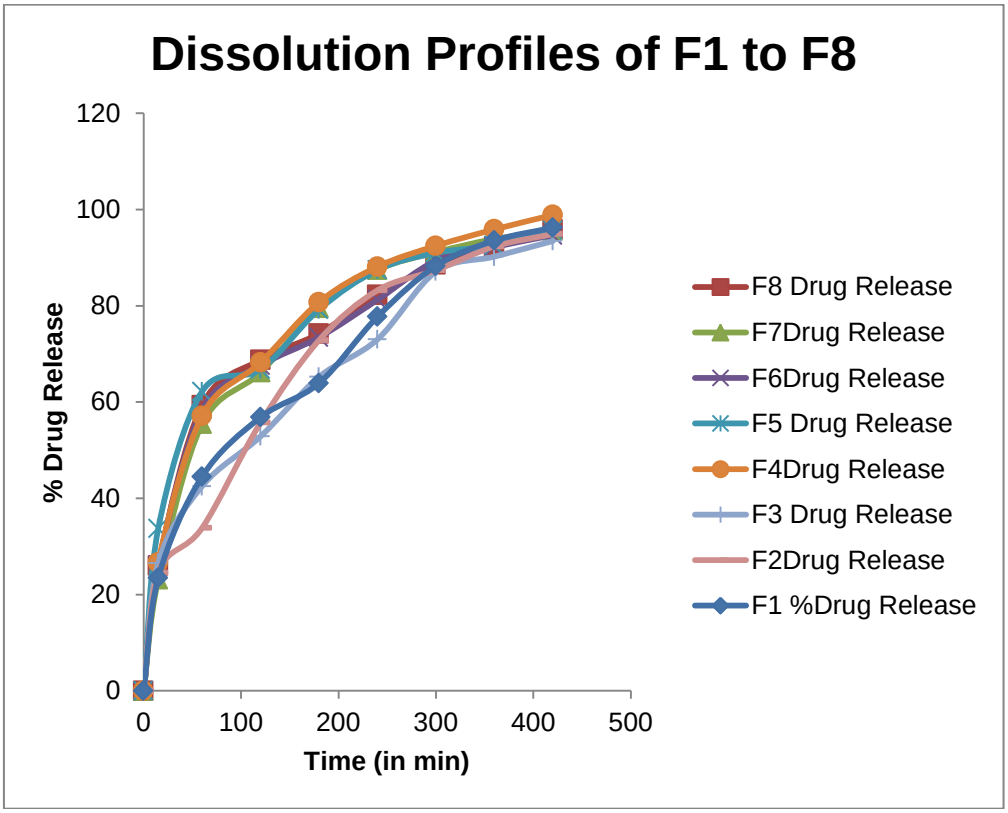

Fig. 6: Graph showing cumulative % drug release

RESULTS AND DISCUSSION

Formulation and evaluation parameters have been performed in satisfactory data. The title of this study is to prolong the bioavailability of the dosage form and to reduce the first pass metabolism. It is a new drug delivery system to maximize effectiveness and compliance. Carvedilol isused in the management of hypertension and angina pectoris and as an adjunct to standard therapy in symptomatic heart failure. The percent drug content of the optimized formulation was found to be 100.02% w/w. hardness of the tablets was found to be in a range of 6.1 to 7.6 kg/cm^2 and it was found that hardness increases with the increase of carbopol proportion in the formulation. The average weight of the tablets was found to be in a range of 101 to 101.44mg and the percent deviation was within a specified limit. Hence all formulations complied with the test for weight uniformity. All the tablets were circular with no visible cracks and smooth on appearance with average thickness of 2.12mm. Further to strengthen these values friability test values were also considered and the weight loss was found to less than 1% in friability test which is considered as an acceptable value for conventional tablets. Thus all tablets complied with IP standards. The welling properties of all the formulations were studied and its results indicate that all the formulations posses a good swelling index. The bioadhesion characteristic were affected by the type and ratio of bioadhesive polymer. The highest bioadhesive force by optimum formulation was found to be 0.95N.

CONCLUSION

Mucoadhesive buccal tablets containing Carvedilol were prepared successfully by direct compression method by using natural binders and were subjected to various evaluation parameters such as Weight variation, Friability, Hardness, Drug Content, Swelling index, In-vitro drug release, In-vitro Mucoadhesive strength. It was revealed that tablets of all batches had acceptable physical parameters. FT-IR studies revealed that there was no interaction between Carvedilol and other excipients used in tablets. Different polymers were selected on the basis of their effect on the retardation release of drug from tablet. The optimized formulation consist of Carvedilol (6.25mg), Carbopol 940P and Chitosan in 3:1 ratio, Cross Carmellose sodium (5mg), magnesium stearate (1.75mg) and talc (2mg) was selected as optimum formulation. From the release studies and Mucoadhesive study, it concluded that these novel formulations can by-pass first pass metabolism and enhance the release for extended period of time.

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