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Formulation and Evaluation of Mucoadhesive Tablets of Acarbose for Type 2 Diabetes

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ABSTRACT

The objective of the study was to develop mucoadhesive tablet of Acarbose (α-glycosidase inhibitor) to enhance the bioavailability and to further reduce the dosing frequency of administration. The Mucoadhesive tablets of Acarbose were prepared by using three different Mucoadhesive polymers such as HPMC E5 LV, Sodium alginate and Guar Gum in varying concentrations and by direct compression technique. The micromeritics evaluation such as angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio showed good to satisfactory flow properties. Swelling index was calculated with respect to time. The swelling index profile of all formulations, prepared as per the experimental design showed an increase in the value of swelling index as the amount of polymer increased. Maximum swelling index was found seen with formulations containing Sodium alginate, the value increases with increasing the amount of sodium alginate. The highest adhesion force i.e. highest strength of mucoadhesive bond was observed with Formulation F9 containing Guar gum as 18.02±0.17, this followed by F6 containing Sodium alginate as 16.33±0.56 and formulation F8 containing Guar gum in the ratio 1:2 as 14.26±0.11. The Adhesion Force increases with increasing the concentration of Mucoadhesive polymers used. The Tablets containing HPMC E5 LV showed least adhesive force than tablets of other formulations. The formulation F6 containing Sodium alginate was taken as optimized formulation based on its mucoadhesive strength and in vitro release was found to be optimum. The optimized formulation was subjected to kinetic drug release studies. The formulation best fitted into zero order kinetics. The drug release was dominated by the erosion and swelling of the polymer. From the release exponent in the Korsmeyer-Peppas model it could be suggested that the mechanism that leads to the release of drug was non-Fickian diffusion.

Key words: mucoadhesive tablet, Acarbose, Gastroretentive

1.INTRODUCTION

Mucoadhesive drug delivery has been a topic of interest in the design of drug delivery system to lengthen the residence time of the dosage form at the site of application or absorption and to facilitate intimate contact of the formulation with the underlying absorption surface, so has to improve and enhance the bioavailability of the drug. Mucoadhesive drug delivery systems are beneficial, since they give a controlled drug release over a period of time and can also be utilized for localization of drug to a specific site in the body. After oral administration, such a stomach-specific mucoadhesive tablets would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract[1].Under certain circumstances prolonging the gastric retention of a delivery system is desirable for achieving great therapeutic benefit of the drug substance. Mucoadhesive polymers are water

soluble and water insoluble polymers, Which are swellable networks, jointed by cross-linking agents. There is an optimum concentration for a mucoadhesive polymer to produce maximum bioadhesion. In highly concentrated system, beyond the optimum level, however the adhesive strength drops significantly because the coiled molecules become separated from the medium so the chain available for interpenetration are not numerous. It affects the availability of long polymer chains for penetration into the mucus layer. Thus it is important mainly for liquid and viscous drug delivery system. For solid dosage forms such as tablets higher the polymer concentration, stronger bioadhesion. When the concentration of polymer is too low, the number of penetrating polymer chains per unit volume of the mucous is small and the interaction between polymers and mucous is unstable.

Acarbose is a competitive inhibitors of the intestinal α-glucosidases and reduce post meal excursions by delaying digestion and absorption of starch and disaccharides. Their mechanism of action being limited to the intestinal brush border membrane, and owing to their structural features, they have limited bioavailability. Therefore, the aim of the present investigation, was to develop mucoadhesive tablet of Acarbose to enhance the bio-availability and to further reduce the dose and frequency of administration.

2.MATERIALS AND METHOD

Acarbose were purchased from Yarrochem products Mumbai. HPMC E5 LV, sodium alginate, Pvp k 30, Lactose was purchased from Nice chemicals, cochin. Guar gum was purchased from Himedia Laborotories. Purified Talc was purchased from Bharath pharmaceuticals Chennai. All the chemicals and reagents used were of analytical grade.

2.1 Preparation of calibration curve

Acarbose equivalent to 100mg was accurately weighted and transfered in to volumetric flask and dissolved in 100ml of 0.1N HCl pH 1.2 to give stock solution containing 1000mg/ml. The stock solution was serially diluted to get 40,50,60,70,80, mg/ml of Acarbose. The absorbance value was plotted against concentration (mg/ml) to obtained the standard calibration curve. The absorbance of each test solution was measured at λ_{max} i.e 204nm of Acarbos in UV/Visible spectroscopy against blank.

2.2 Preparation of Acarbose mucoadhesive tablet

Acarbose Mucoadhesive buccal tablets were prepared by Direct compression technology. Before going to direct compression all the powders passed through a 60 mesh sieve. The required quantity of drug, various polymer mixtures and fillers were mixed thoroughly. The blend was lubricated with magnesium stearate for 3-5mins and talc was added as glidant. The blend was directly compressed (8 mm diameter, round flat faced punches) using multiple punch tablet compression machine .Each tablet contained 25mg of Acarbose.

Table 1: Composition of various batches of mucoadhesive tablets of Acarbose

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Acarbose	25	25	25	25	25	25	25	25	25
Hpmc E5	25	50	75	-	-	-	-	-	-
Sodium alginate	-	-	-	25	50	75	-	-	-
Guar-Gum	-	-	-	-	-	-	25	50	75
Pvp k30	10	10	10	10	10	10	10	10	10
Lactose	70	44	20	70	44	20	70	44	20
MCC	10	10	10	10	10	10	10	10	10
Magnesium state	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Total weigh	150	150	150	150	150	150	150	150	150

2.3 Pre compression evaluation

Flow properties and compressibility properties of powder mixture were evaluated by measurement of angle of repose, bulk density, carr's index and hausner's ratio.

2.3 Determination of drug content.[2]

Five tablets from each formulation were taken, crushed in a mortar and mixed. From the mixture quantity equivalent to 100 mg of Acarbose was accurately weighted and extracted thoroughly with a 100 ml of 0.1N HCL (pH 1.2) .The Contends were shaken periodically and kept for 24hs for solvation of drug completely. The mixture was filtered and the amount of drug present in each extract was determined using UV spectrometer at 204nm against blank reference. The procedure was repeated thrice and this average was chosen..[2]

2.4 Swelling Index

Swelling index were determined for each formulation batch, one tablet was weighed and placed in a beaker containing 200ml of 0.1N HCL. After each interval the tablet was removed from the beaker and weighed again up to 8 hours. The swelling index was calculated using following formula.

Swelling Index(S.I)=$(W_t - W_0) / W_0$

Where S.I = Swelling index.

W_t = Weight of tablet at time t.

W_0 = Weight of tablet before placing in the basket.

2.5 Measurement of adhesive force[3]

Two sides of the balance were balanced with 15 gm weight on the right hand side. The goat gastric mucus membrane was used as the model membrane and pH 1.2 0.1N HCl was used as the moistening fluid. The goat stomach mucosa was kept in tyrode solution at 37^0c for 2 hr. The underlying mucus membrane was separated and washed thoroughly with 0.1N HCl and attached with the mucosal side upward over the stainless steel block (2). it was then placed in to the glass container filled with 0.1 N HCl ,such that the HCl reaches the surface of the mucosal membrane and keep it moist. This was then kept below the left hand side of the balance, the tablet was then stuck with little moisture to the stainless steel block 1 hanging on the left hand side and the beam is raised with a 15 gm weight on the right pan removed. This lowers the stainless steel block1 along with the tablet over the mucosa with a weight of 15 gms. The balance was kept in this position for 3 min and then slowly weights were added on the right pan till the tablet separated from the mucosal surface. The excess weight on the pan (i.e, the total weight minus 15 gm) is the force required to separate the tablet from the mocosa. The bioadhesive strength of the tablet is represented in grams. Three tablets were tested from each batch. After each measurement the tissue was gently and thoroughly washed with saline and left for 15 min before the next measurement. Fresh tissue was used for each batch of tablets

Fig:1Modified physical balance for the determination of mucoadhesive strength

2.6 In-vitro drug Release study[4]

The in-vitro Drug Release study was performed using USP dissolution Rate test apparatus (paddle type; 50 Rpm).Dissolution study carried out for 12 hrs 0.1N HCl (pH 1.2 900ml) was used as dissolution media during the course of study whole assembly was maintained at 37±0.5℃. Sample of each 5 ml were withdrawn after every 1 hr for a period

of 12 hr and the volume in dissolution vessel was kept constant by equal replacement with fresh media. The withdrawn sample were diluted with dissolution medium and then filter it with Whatman filter paper. The sample were collected in test tubes. The amount of the drug in the aliquots was quantified by taking the Absorbance of the sample at 204nμ spectrophotometrically using 0.1 N HCl (dissolution media) as blank

3. RESULT AND DISCUSSION

Graph1: Standard graph of Acarbose at 0.1N HCL of pH 1.2

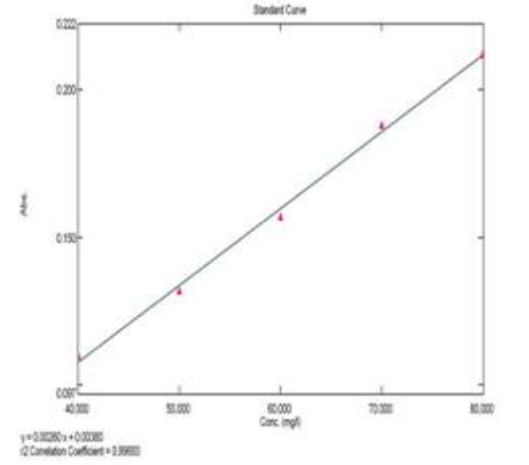


Table 2: Standard curve of Acarbose

Concentration(μg/ml)	Absorbance(nm)
40	0.110
50	0.132
60	0.157
70	0.188
80	0.212

Graph2: Determination of λ_{max} of Acarbose λ_{max} of Acarbose was found to be 204nm

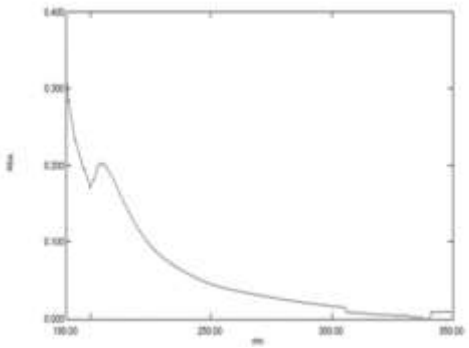


Figure 2: FTIR Spectra of Acarbose, HPMC E5 LV, and Acarbose-HPMC E5

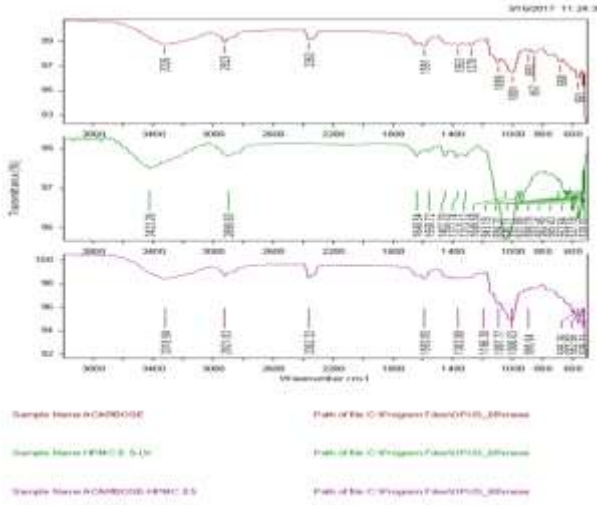


Figure 2: FTIR spectra of Acarbose, PVP K_{30} and Acarbose-PVP K_3

Figure 3: FTIR spectra of Acarbose, PVP K_{30} and Acarbose-PVP K_3

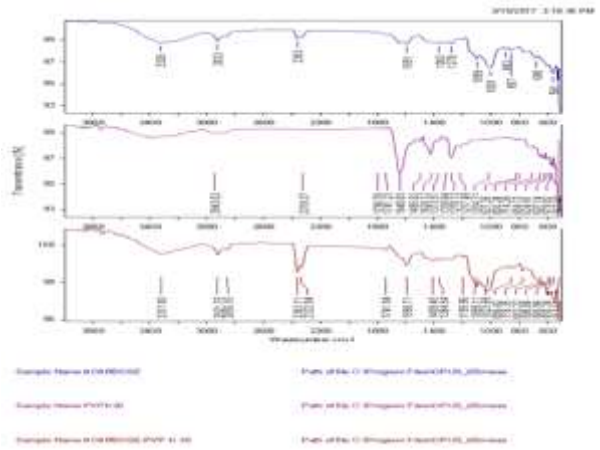


Figure 3: FTIR Spectra of Acarbose, Guar Gum and Acarbose-Guar Gum

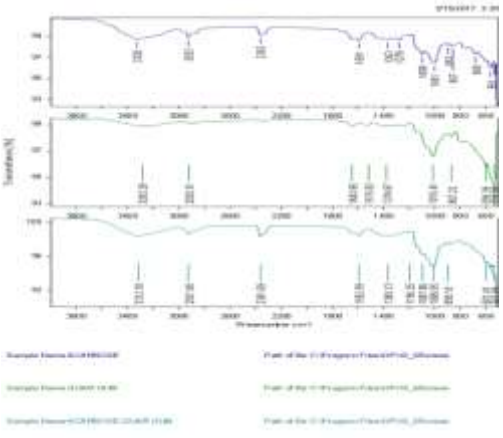


Figure 5: FTIR Spectra of Acarbose, Sodium Alginate and Acarbose -Sodium Alginate

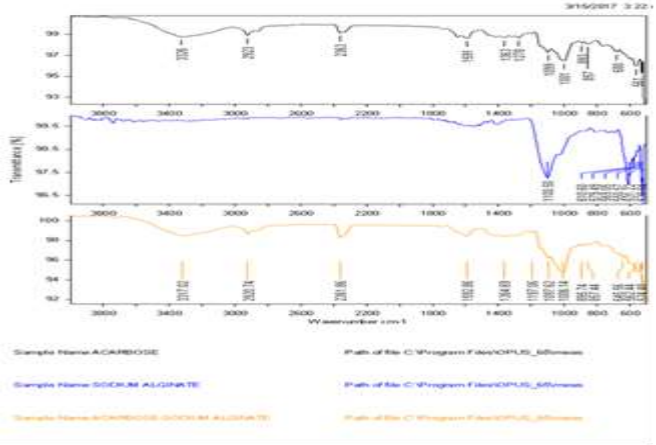


Table 3: Result of pre-compression properties of Acarbose

Formulation code	Angle of repose(º)	Bulk density (g/cm3)	Tapped density (g/cm3)	Compressibilityindex(%)	Hausner ratio
F1	33.15	0.49	0.59	16.94	1.20
F2	33.36	0.50	0.57	12.28	1.14
F3	31.31	0.50	0.58	13.79	1.16
F4	32.24	0.52	0.59	11.86	1.13
F5	31.13	0.51	0.61	16.39	1.19
F6	32.24	0.50	0.57	12.28	1.14
F7	33.52	0.50	0.58	13.79	1.16
F8	31.30	0.50	0.58	13.79	1.16
F9	30.45	0.50	0.57	12.28	1.14

Table 4: Result of post compression properties of Acarbose mucoadhesive tablets

Formulation code	Weight variation (mg)	Friability (%)	Hardness(kg/cm^2)	Average thickness (mm)	Percentage drug content (%)
F1	153.49±1.21	0.66±0.012	3.5±0.17	2.78±0.055	87.86±0.053
F2	149.68±2.08	0.52±0.021	3.3±0.08	2.72±0.025	84.60±0.066
F3	151.31±1.12	0.58±0.014	3.4±0.17	2.74±0.028	91.40±0.082
F4	149.45±1.70	0.48±0.017	3.5±0.21	2.77±0.049	88.33±0.061
F5	148.39±1.43	0.42±0.025	3.4±0.08	2.76±0.033	87.33±87.15
F6	149.41±1.49	0.56±0.040	3.3±0.14	2.73±0.024	89.80±0.033
F7	152.92±1.47	0.49±0.035	3.4±0.45	2.69±0.018	84.75±0.13
F8	153.48±2.46	0.61±0.029	3.5±0.38	2.72±0.020	86.40±0.235
F9	150.03±1.78	0.44±0.024	3.5±0.58	2.74±0.017	82.06±0.971

Table 5: Result of Swelling index of Acarbose mucoadhesive table

Formulation code	Time in hours				
	2hrs	4 hrs	6 hrs	8 hrs	
F1	44.66±0.871	86.75±1.360	138.41±1.654	158.27±1.323	
F2	46.97±0.832	91.27±1.452	143.33±1.364	165.01±1.451	
F3	47.01±1.090	90.66±1.932	145.33±0.843	167.11±0.943	
F4	72.84±1.077	156.66±1.085	191.44±1.638	215.33±1.134	
F5	77.33±1.129	160.40±0.547	196.02±1.126	217.33±1.632	
F6	78.80±1.800	158.27±1.427	204.02±1.138	218.66±1.368	
F7	69.73±0.818	153.64±0.827	193.33±1.061	211.33±1.438	
F8	73.33±1.284	152.63±0.823	197.35±0.826	210.59±1.356	
F9	76.15±0.538	156.29±1.077	198.01±1.123	213.90±1.120	

Table 6: Result of determination of bioadhesive strength

SI no:	Formulation code	Mucoadhesive strength
1	F1	8.15±0.07
2	F2	11.61±0.87
3	F3	13.60±0.65
4	F4	10.10±0.12
5	F5	11.54±0.15
6	F6	16.33±0.56
7	F7	12.40±0.24
8	F8	14.26±0.11
9	F9	18.02±0.17

Table 7: In-vitro Dissolution studies

Time in Hrs	% CUMULATIVE DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	13.93	8.86	9.78	12.73	11.16	10.70	9.32	9.27	7.93
2	19.47	19.47	13.01	18.64	16.70	12.09	13.47	11.63	10.24
3	25.01	27.78	17.63	27.73	20.86	19.01	16.24	15.78	14.86
4	42.09	31.47	22.24	33.13	24.09	23.16	17.16	16.24	15.32
5	51.32	45.18	25.47	37.61	25.93	33.32	20.86	19.93	18.09
6	56.86	50.86	33.78	40.24	37.01	45.32	23.63	21.78	26.86
7	64.24	55.01	47.16	48.50	48.55	47.63	32.86	31.93	30.09
8	69.32	57.78	52.70	54.13	54.55	60.09	46.24	45.78	39.32
9	73.93	67.15	57.32	60.96	59.63	72.09	50.86	49.93	48.55
10	79.93	73.10	63.78	75.32	64.70	73.01	55.47	53.63	55.93
11	88.24	76.24	71.63	86.95	82.24	81.78	70.24	69.78	71.63
12	95.63	86.86	85.01	93.18	87.78	87.32	82.24	80.86	76.70

Fig 6: Dissolution profile of different batches of Acarbose mucoadhesive tablets

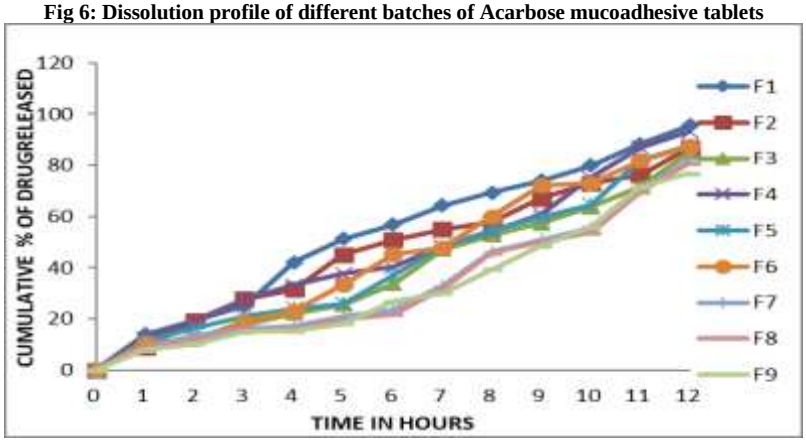


Fig 7: Dissolution Study of Optimized Formulation (F6) Of Prepared Mucoadhesive tablets of Acarbose

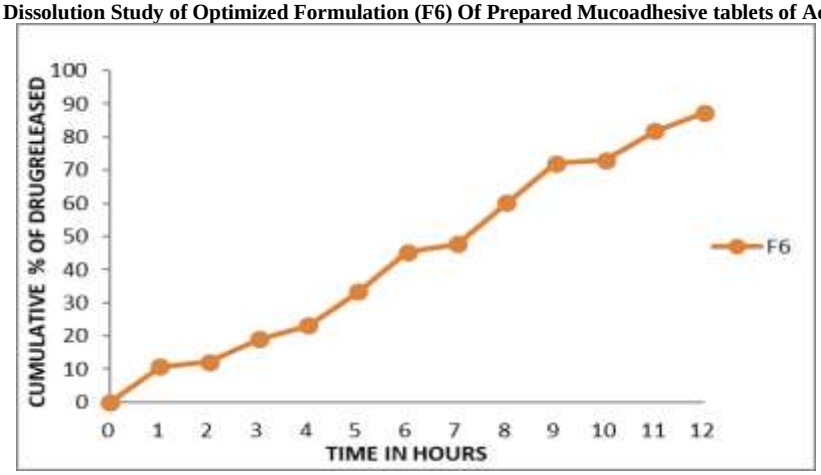
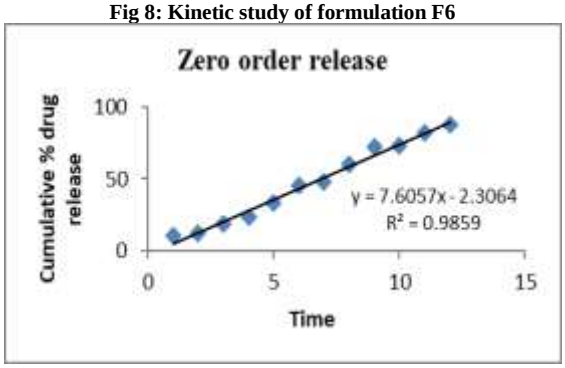


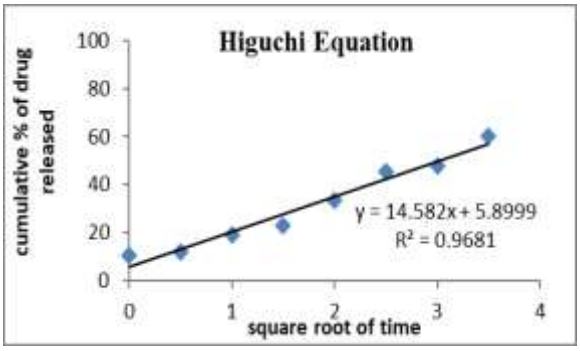
Table 8: Kinetic Release Studies

Time(hrs)	%CDR	log%CDR	%DRTR	Log%DRTR	Square root of time	Log time
1	10.70	1.0296	89.2924	1.950814	1	0
2	12.09	1.0825	87.9077	1.944026	1.414213	0.30102
3	19.01	1.2791	80.9847	1.908402	1.732050	0.47712
4	23.16	1.3649	76.8308	1.885535	2	0.60205
5	33.32	1.5227	66.677	1.823976	2.236067	0.69897
6	45.32	1.6563	54.677	1.737804	2.449489	0.77815
7	47.63	1.6778	52.3693	1.719076	2.6457513	0.84509
8	60.09	1.7788	39.9077	1.601056	2.828427	0.90308
9	72.09	1.8578	27.9077	1.445724	3	0.95424
10	73.01	1.8634	26.9847	1.431117	3.1622776	1
11	81.78	1.9126	18.2154	1.260438	3.316624	1.04139
12	87.32	1.9411	12.677	1.103016	3.464101	1.0791

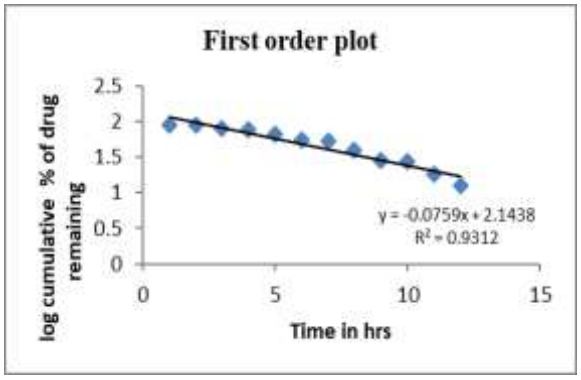
Fig 8: Kinetic study of formulation F6



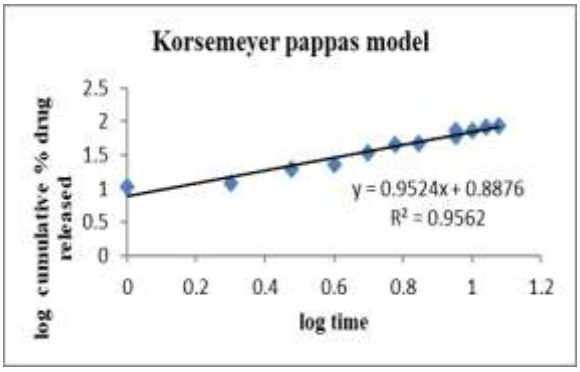
The higher correlation coefficient suggests that the drug release from the formulation follows is zero order kinetics



The poor correlation coefficient suggest that the drug release does not follow Higuchi kinetics.



The poor correlation coefficient suggest that the drug release does not follow first order kinetics.



The value of release component (n) was found 0.9524, suggesting non-Fickian diffusion.

Table 9: kinetic modelling

Formulation	Zero order	First order	Higuchi	Korsmeyer pappas	
F6	Correlation coefficient (r^2)	Correlation coefficient (r^2)	Correlation coefficient (r^2)	Release Exponent (n)	Correlation coefficient (r^2)
	0.9859	0.9312	0.9681	0.9524	0.9562

CONCLUSION

Mucoadhesive buccal tablets of Acarbose were prepared by direct compression method. Different polymers and ingredients in different ratios were tried to select optimum formulation. The micromeritics evaluation showed good to satisfactory flow properties. Maximum swelling index was found seen with formulations containing Sodium alginate, the value increase as the amount of polymer increased. The comparison of drug release profile of all formulations, showed that formulation F1 containing HPMC E5 LV show maximum drug release and formulation containing Guar gum show slow drug release. The highest adhesion force was observed with Formulation F9 containing Guar gum as 18.02±0.17 this followed by F6 containing Sodium alginate as 16.33±0.56 and formulation F8 containing Guar gum as 14.26±0.11.The Adhesion Force Increases with increasing the concentration of Mucoadhesive polymers used. The Tablets containing HPMC E5 LV showed least adhesive force than tablets of other formulations.

The formulation F6 containing Acarbose and sodium alginate in the ratio 1:3 was selected as optimum formulation, based on its mucoadhesive strength and *in vitro* release was found to be optimum.

The optimized formulation was subjected to kinetic drug release studies. The formulation best fitted into Zero order kinetics. The drug release was dominated by the erosion and swelling of the polymer. From the release exponent in the Korsmeyer-Peppas model it could be suggested that the mechanism that leads to the release of drug was non -Fickian diffusion.

Overall evaluation of the mucoadhesive behaviour of the nine formulations indicating sufficient mucoadhesive strength likely to increase its residence time in the Gastrointestinal tract, which eventually improve the extent of bioavailability. *In vitro* drug release studies of the nine formulation examined showed a controlled pattern of drug release up to 12 hrs. Thus, the proposed work would become a platform for developing the antidiabetic drug into a novel drug delivery system.

Declaration by Authors

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