Research Article

Formulation and Evaluation of Mucoadhesive Buccal Tablets of Repaglinide

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ABSTRACT

Objective: Delivery of the desired drug as mucoadhesive drug delivery systems has been subject of interest since 1980s. The various advantages associated with these systems made the buccal drug delivery as a novel route of drug administration. Buccal region offers an attractive route for the administration of systemic drug delivery. The objective of the study was to develop mucoadhesive buccal tablets of repaglinide. **Methodology:** The tablets were prepared by wet granulation method using a combination of mucoadhesive polymers like chitosan, hydroxyethyl cellulose, guar gum and carbopol 934P in different ratios. **Results:** Buccal tablets were evaluated by different methods for parameters such as thickness, hardness, weight uniformity, drug content uniformity, surface pH, *ex vivo* mucoadhesive strength, *ex vivo* residence time, *in vitro* drug release, *ex vivo* drug permeation. The tablets were evaluated for *in vitro* release in phosphate buffer of pH 6.8 for 12 h. In order to determine the mode of release, the data was subjected to zero order, first order, Higuchi and Korsmeyer-Peppas model. The mucoadhesive strength was evaluated by measuring the force required to detach the tablets from sheep buccal mucosal membrane. Carbopol 934P showed maximum mucoadhesion and required maximum force for detachment; the force required for detachment was directly proportional to its content. DSC and XRD study of the pure drug indicated that the drug is in the crystalline form. But in the formulations, peaks indicated that the drug is in the amorphous form. FTIR spectroscopic studies indicated that there is no drug-excipient interaction. **Conclusion:** The prepared formulations showed good mucoadhesive strength and ability to sustain the drug release over 12 h; hence, these are the versatile drug delivery systems for repaglinide.

Key words: Mucoadhesive buccal tablet, Chitosan, Mucoadhesive strength, Repaglinide, Carbopol 934P, *ex vivo* drug permeation.

INTRODUCTION

Amongst various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike.[1] In present study, repaglinide was used as a model drug for buccal drug delivery system, as it has good absorption through oral cavity.[2] Mucoadhesive polymers are able to interact with mucus, which is secreted by the underlying tissue. The concept of mucoadhesive polymer has been accepted as a promising strategy to prolong the resident time and to improve the specific localization of drug delivery systems on various membranes.[3]

The buccal drug delivery systems have certain advantages such as it avoids first pass effect, improves oral bioavailability, gives painless administration, possibility of easy drug withdrawal and have superior patient compliance. In addition, it releases the drug towards the mucosa in a controlled and predictable manner to elicit the required therapeutic response.[4] Therefore; the oral mucosa may be potential site for the buccal controlled drug delivery.[5]

Repaglinide is a non-sulfonylurea oral hypoglycaemic agent of the meglitinide class; it is mainly used in the management of type II diabetes mellitus.[2] It has short biological half-life of less than one hour and rapidly eliminated from the body. It is a BCS

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class II compound and the bioavailability following oral administration is low (56%), BCS class II compounds are poorly soluble but highly permeable and they exhibit bioavailability that is limited by dissolution rate.

Singh *et al*. reported that the buccal tablets of repaglinide, which were prepared with the aim of avoiding the first pass metabolism as well as to evaluate the sustained release component of microcrystalline chitosan and compared with the carbopol. The buccal tablets were prepared using different composition of microcrystalline chitosan as a primary polymer and HPMC K4M, sodium carboxymethyl cellulose and karaya gum as secondary polymers. The tablets containing combination of microcrystalline chitosan and sodium carboxymethyl cellulose show significant mucoadhesive performance and *in vitro* drug release.[6]

But, in the present study, we have used a combination of chitosan, hydroxyethyl cellulose, guar gum and carbopol for the development of buccal tablets for repaglinide. Therefore, objective of the present study was the design and evaluation of mucoadhesive buccal tablets of repaglinide using the above said polymers to overcome the bioavailability related problems, to reduce dose dependent side effects and frequency of administration.[7] Prolonged retention of drug in the buccal cavity improves its absorption and the bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment.[8]

MATERIALS AND METHODS

Repaglinide was gifted and Hydroxyethyl cellulose (HEC) was purchased from Yarrow Chem. Products, by Biocon Lab. Pvt. Limited, Bangalore. Polyvinyl Pyrrolidone K30 (PVP) was purchased from Sisco Research Laboratories Pvt. Ltd. Mumbai. Chitosan (CH) and Gaur gum (GG) were purchased from Himedia Lab. Pvt. Ltd, Mumbai. Carbopol 934P (CP) was purchased from Ozone International, Mumbai. All other materials were of analytical or pharmacopoeial grade and used as received.

Preparation of mucoadhesive tablets

Wet granulation method was employed to prepare buccal tablets of repaglinide using chitosan, HEC, Guar Gum and Carbopol 934P as polymers.[9] Mucoadhesive matrix tablets each containing 15 mg of repaglinide were prepared by non-aqueous granulation method (using Isopropyl alcohol). All the ingredients except lubricants were mixed in the order of ascending weights and blended for 10 min in an inflated polyethylene was done with binder solution of PVP K30 which was previously dissolved in isopropyl alcohol; this damp mass was passed through sieve No. 16. The granules were dried at pouch and repaglinide was added in this mixture and mixed for 2 min. Granulation 40° for 30 min and then passed through Sieve No. 22-44 and lubricants such as magnesium stearate and talc were mixed and then compressed with a 10 station rotary compression machine into 100 mg tablets to a hardness of 5-7 kg/cm^2 using 6 mm punch. All the prepared tablets were evaluated for drug content uniformity, friability, hardness and weight variation. Composition of the prepared mucoadhesive buccal tablet formulations of repaglinide is given in Table 1.

Evaluation of granules for buccal tablets of repaglinide

The prepared granules were evaluated for bulk density, tapped density, angle of repose, Hausner's ratio and Carr's index.[10,11]

Table 1: Composition of buccal tablets of repaglinide

Ingredients/ Formulation Code	Repaglinide (mg)	Chitosan (mg)	HEC (mg)	Guar Gum (mg)	Carbopol (mg)	Lactose (mg)	Mg. Stearate (mg)	Talc (mg)	Methyl Paraben (mg)	Total weight (mg)
BU1	15	20	40	-	-	21	1	2	1	100
BU2	15	20	-	40	-	21	1	2	1	100
BU3	15	20	-	-	40	21	1	2	1	100
BU4	15	-	10	20	-	51	1	2	1	100
BU5	15	-	10	-	20	51	1	2	1	100
BU6	15	-	-	20	40	21	1	2	1	100
BU7	15	40	20	-	-	21	1	2	1	100
BU8	15	40	-	20	-	21	1	2	1	100
BU9	15	40	-	-	20	21	1	2	1	100
BU10	15	-	20	10	-	51	1	2	1	100
BU11	15	-	20	-	10	51	1	2	1	100
BU12	15	-	-	40	20	21	1	2	1	100

Fourier Transform Infrared Spectroscopy

The samples were crushed with KBr to make pellets under hydraulic pressure of 10 tons, and then the FTIR spectra were recorded between 400 and 4000 cm^{-1}.

Differential scanning calorimetric analysis

The samples were heated from 0-300° at a heating rate of 10°/m under argon atmosphere using a microcalorimeter and then thermograms were obtained.

Physical evaluation

According to the methods mentioned in monograph of repaglinide tablets, the thickness, weight variation, hardness of formulations BU1 to BU12 were studied using digital micrometer, electronic balance and Pfizer hardness tester respectively.[12,13]

Friability test

The friability of tablets was determined by using Veego Friabilator. It was expressed in percentage (%). Twenty tablets were initially weighed ($W_{initial}$) and transferred to friabilator. The friabilator was operated at 25 rpm for 4 m or run up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated by;

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

Drug content uniformity

Ten tablets were weighed and powdered. An amount of the powder equivalent to 15 mg of repaglinide was dissolved in 100 ml of phosphate buffer of pH 6.8, filtered, diluted suitably and analyzed for drug content at 241 nm using UV-Visible spectrophotometer.

Measurement of surface pH

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects *in vivo*. An acidic or alkaline pH may irritate the buccal mucosa; we sought to keep the surface pH as close to neutral as possible. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping in contact with 5 ml of distilled water (pH 6.8 ± 0.05) for 2 h and pH was noted by bringing the electrode in contact with the surface of the formulation and allowing it to equilibrate for 1 m. This test was done in triplicates and mean was calculated.[14]

Mucoadhesion strength

The apparatus used for testing bioadhesion was assembled in the laboratory. Mucoadhesion strength of the tablet was measured on a modified physical balance. A double beam physical balance was taken and the left pan was removed. To left arm of balance, a thick thread of suitable length was hanged. To the bottom side of thread a glass vial of 30 ml capacity with uniform surface was tied. A clean 500 ml glass beaker was placed below hanging glass vial within which was placed another glass beaker of 100 ml capacity in inverted position. The temperature control system involves placing thermometer in 500 ml beaker and intermittently adding phosphate buffer solution (37°) of pH 6.8 in 500 ml beaker the balance was so adjusted that right hand side was exactly 5 g heavier than the left.

The balance adjusted as described above was used for the study. The sheep buccal mucosa, excised and washed was tied stuck with mucosal side upward using cyanoacrylate adhesive over the base of inverted 100 ml glass beaker. This beaker weighed and lowered into 500 ml beaker, which was then filled with isotonic phosphate buffer (pH 6.8) and kept at 37°, such that the buffer reaches the surface of mucosal membrane to keep it moist. This was then kept below left hand side of balance. The buccal tablet was then stuck to glass vial using cyanoacrylate adhesive. The 5 g on right hand side was removed; this caused application of 5 g pressure on buccal tablet overlying moist mucosa. The balance was kept in this position for 3 min. and then slowly weights were increased on the right pan until the tablet separates from mucosal membrane. The total weight on right pan minus 5 g gave the force required to separate tablet from mucosa. This gave bioadhesive strength in grams. The mean value of three trials was taken for each set of formulations. After each measurement, the tissue was gently and thoroughly washed with isotonic phosphate buffer and left for 5 minutes before studying a new tablet of same formulation to get reproducible multiple results for the formulation.[15,16]

In vitro drug release study

This was carried out in USP tablet dissolution test apparatus (Electrolab TDT-08L), employing paddle stirrer at 50 rpm and 900 ml of pH 6.8 phosphate buffer was used as dissolution medium. The release study was performed at 37 ± 0.5°. Samples of 5 ml were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were analyzed for repaglinide by measuring the absorbance at 241 nm using Shimadzu- 1700 UV- Visible Spectrophotometer.[17] The data obtained from *in vitro* release study were fitted into four models

- Cumulative percent drug released versus time (zero order kinetic model)
- Log cumulative percent drug remaining versus time (first- order kinetic model)
- Cumulative percent drug released versus square root of time (Higuchi's model)

Figure 1: Modified disintegration apparatus for measurement of *ex-vivo* residence time

- Log cumulative percent drug released versus log time (Korsmeyer-Peppas equation)

Determination of ex vivo residence time

The ex vivo residence time was determined using a locally modified USP disintegration apparatus. The disintegration medium composed of 800 ml pH 6.8 phosphate buffer maintained at 37°. The sheep buccal tissue was glued to the surface of a glass slab using cyanoacrylate adhesive and vertically attached to the apparatus. The buccal tablet was hydrated from one surface using 0.5 ml of pH 6.8 phosphate buffer and then the hydrated surface was brought in contact with the mucosal membrane. The glass slide was vertically fixed to the apparatus and allowed to run in such way that the tablet completely immersed in the buffer solution at the lowest point and was out at the highest point. The time taken for complete erosion or dislodgment of the tablet from the mucosal surface was noted.[18] Modified disintegration apparatus is shown in Figure 1.

In vitro permeation studies

It is essential to investigate the permeation of the drug molecule through the appropriate buccal mucosa to ascertain the systemic availability of the drug molecule from the developed buccal adhesive system. This study was carried out by using modified version of a diffusion cell. It consisted of a glass tube open at both ends. Sheep buccal mucosa was chosen as the model membrane, glued with mucosal side facing upward at one end of the diffusion cell. The end containing mucosal membrane was dipped carefully in a beaker containing 100 ml of phosphate buffer of pH 6.8. This beaker was placed on magnetic stirrer with heating plate. The beaker content was maintained at 37 ± 0.5° and stirred with a magnetic bead. The tablet was stuck on the sheep buccal membrane which was previously moistened with a 2 ml of simulated salivary fluid. Samples of 5 ml were withdrawn from the beaker at a pre-determined time intervals and then analyzed for repaglinide at 241 nm with suitable dilutions.[19,20] The sheep buccal tissue was obtained from registered slaughter house of Bijapur city (Reg. No. 903611).

RESULTS AND DISCUSSION

The main goal of this work was to develop new mucoadhesive tablets of repaglinide. In the present work, mucoadhesive buccal tablets of repaglinide were prepared by wet granulation using mucoadhesive polymers like CH, HEC, GG, CG in different ratios. According to work plan, the tablets were evaluated for their thickness, hardness, friability, weight variation, surface pH, drug content, mucoadhesive strength, *in vitro* release.

Repaglinide buccal tablets were prepared using chitosan and HEC (BU1 & BU7), chitosan and guar gum (BU2 & BU8), chitosan and carbopol (BU3 & BU9), HEC and guar gum (BU4 & BU10), HEC and carbopol (BU5 & BU11) and guar gum and carbopol (BU6 & BU12). The granules were evaluated for bulk density, tap density and angle of repose. The results of bulk density and tap density were in the range of 0.292 g/cc to 0.595 g/cc and 0.331 g/cc to 0.681 g/cc respectively. The granules exhibit good flow properties, as the angle of repose values were less than 30°. A good packing ability of the granules was indicated by Carr's compressibility index and Hausner's ratio. The results are shown in Table 2.

All the prepared mucoadhesive buccal tablets of repaglinide were evaluated for thickness, hardness, friability, weight variation and uniformity of drug content and data is shown in Table 2. The hardness of prepared mucoadhesive buccal tablets was in the range of 4.9 to 5.8 kg/cm^2 and hardness was increased as the concentration of carbopol was increased in the formulation. The thickness of the tablets was in the range of 2.71 to 2.91

Table 2: Data obtained from evaluation of granules and tablets

Formulation Codes	Bulk Density (g/cc)	Tap Density (g/cc)	Carr's Index (%)	Hausner Ratio (%)	Angle of Repose (°)	Hardness (kg/cm²)*	Friability (%)	Thickness (mm)*	Drug content (%)*	Weight variation (mg)*
BU1	0.415	0.481	13.72	1.15	29.53	5.06	0.69	2.833	94.32	0.107
BU2	0.395	0.420	5.95	1.06	28.07	5.76	0.53	2.852	94.87	0.103
BU3	0.340	0.392	13.26	1.15	27.24	5.85	0.16	2.732	99.17	0.105
BU4	0.493	0.569	13.35	1.15	27.40	5.43	0.98	2737	94.50	0.104
BU5	0.595	0.681	12.64	1.14	29.24	4.96	0.36	2.811	95.05	0.104
BU6	0.420	0.496	15.32	1.18	28.73	5.83	0.19	2.759	97.80	0.101
BU7	0.292	0.331	11.78	1.18	30.69	5.53	0.93	2.912	95.87	0.103
BU8	0.356	0.395	9.87	1.10	27.24	5.56	0.38	2.713	94.50	0.102
BU9	0.319	0.349	8.59	1.09	28.73	5.73	0.36	2.878	95.60	0.104
BU10	0.467	0.537	13.03	1.14	28.60	5.33	0.91	2.718	95.60	0.103
BU11	0.530	0.608	12.82	1.14	27.40	5.03	0.35	2.741	95.87	0.105
BU12	0.452	0.520	13.07	1.15	27.55	4.92	0.17	2.842	95.05	0.105

*Average of three determinations

mm, which shows uniform thickness of the tablets. The friability was in the range of 0.16% to 0.98%. Less than 1% indicates good mechanical strength to withstand the rigors of handling and transportations. Weights of the prepared buccal tablets were found to be in the range of 101 to 107 mg. The drug content was in the range of 94.32% to 99.17%, suggesting uniform mixing of drug.

The prepared mucoadhesive buccal tablets were evaluated for *in vitro* residence time using sheep buccal mucosa and the results are presented in Table 3. *In vitro* residence time is the time necessary for complete detachment or erosion of tablet from mucosal surface without losing integrity. Among the 12 formulations subjected for this study, BU3 & BU6 showed maximum residence time of 7 h & 34 m and 6 h & 18 m. It was found that an increase in concentration of carbopol increases the *in vitro* residence time. This is mainly due to the strong mucoadhesive nature of carbopol.

The mucoadhesive strength of prepared mucoadhesive buccal tablets was studied using sheep buccal mucosa and the mucoadhesive parameters were presented in Table 3. The mucoadhesion of all buccal tablets were tested and weight required to pull off the formulation from the mucous tissue was recorded as mucoadhesion strength in grams. The mucoadhesivity of buccal tablets was found to be maximum in case of formulation BU3 and BU6 and it was 31.00 & 34.00 g respectively. This may be due to fact that the positive charges on surface of carbopol could give rise to strong electrostatic interaction with negatively charged mucus membrane.

The surface pH was determined in order to investigate the possibility of any side effects in the oral cavity as acidic or alkaline pH is bound to cause irritation to the buccal mucosa. Surface pH of all formulations was found to be in the range of 6.4 to 6.8 which are nearer to the salivary pH 6.8 (Table 3). Hence, it is assumed that these formulations do not cause any irritation and discomfort to the mucous layer of oral cavity.

The DSC thermograms of plain repaglinide, drug-loaded BU1, BU4 & BU6 tablets and drug-free BU6 are shown in Figure 2. The drug-free tablets show an endothermic peak at 151.3°, whereas drug-loaded tablets showed an endothermic peak at 152.1°, 150.9° & 153.5°. The plain repaglinide has shown a sharp endothermic peak at 137.8° due to melting of the drug, but this peak has disappeared in the formulation. Which clearly suggest that the drug was dispersed uniformly throughout the formulation and the drug has undergone physical complexation with the polymer used?

Table 3: *In vitro* residence time, mucoadhesive strength, and surface pH

Formulation Code	*In vitro* Residence Time (hr)	Mucoadhesive Strength (g)*	Surface pH*
BU1	15 m 29 s	21.66	6.4
BU2	3 h 56 m	23.00	6.7
BU3	7 h 34 m	31.00	6.8
BU4	2 h 26 m	26.66	6.7
BU5	1 h 39 m	23.00	6.7
BU6	6 h 18 m	34.00	6.8
BU7	15 m 59 s	21.00	6.4
BU8	3 h 18 m	22.00	6.5
BU9	20 m 59 s	26.66	6.7
BU10	2 h 11 m	22.66	6.6
BU11	25 m 56 s	23.00	6.8
BU12	5 h 15 m	22.66	6.7

*Average of three determinations

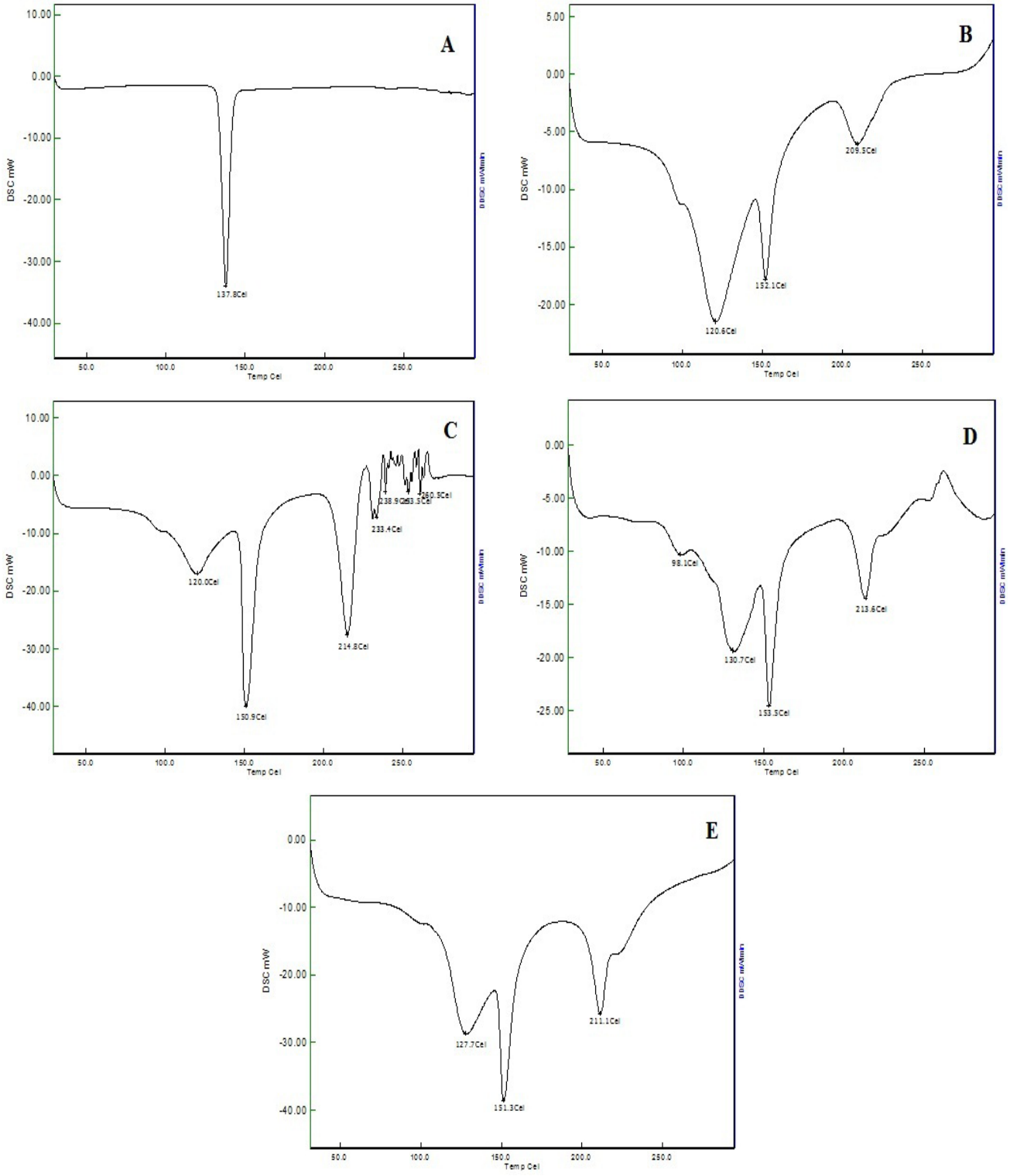

Figure 2: DSC thermograms of pure drug (A), BU1 (B), BU4 (C), BU6 (D), BU6 dummy (E)

The drug-polymer interaction was studied using FTIR spectroscopy for selected combination of drug with different polymers used. The FTIR spectra obtained is illustrated in Figure 3. The peaks, which are seen in the FTIR spectrum of pure drug, have also appeared in the spectrum of drug with other polymers with very slight variations. Hence, the drug is stable in the formulations. All spectra show major peaks such as amide peak near 2400 frequencies and carbonyl peak near 1600 frequency.

The XRD profiles are presented in Figure 4. The pure drug has shown peaks in between the 2θ of 5° and 30° due to the crystalline nature of drug. But the formulations BU1, BU4, BU6 and BU6 dummy have not shown peaks related to drug. Hence, the drug in the formulations is in amorphous form.

The *in vitro* release of repaglinide was performed in phosphate buffer pH 6.8. The *in vitro* release data

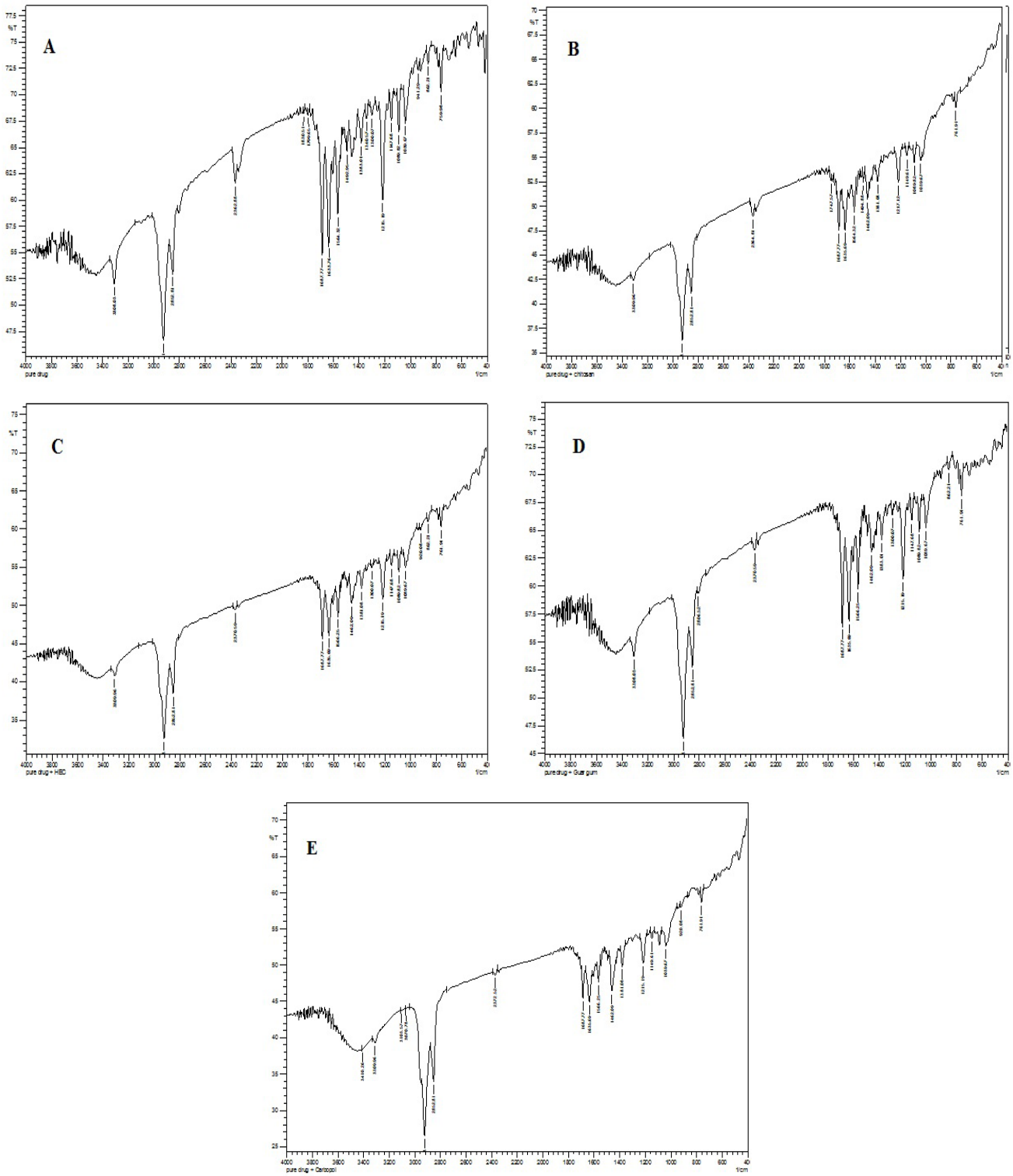

Figure 3: FTIR spectra of repaglinide (A), Drug + Chitosan (B), Drug + HEC (C), Drug + Guar Gum (D), Drug + Carbopol (E)

is depicted in Figures 5 and 6. The *in vitro* release of repaglinide was mainly affected by the drug polymer ratio, nature and amount of polymer and the dissolution medium. The *in vitro* release of repaglinide was also depends on swelling behaviour of the polymers used. From dissolution data, it was evident that designed formulations have shown the drug release in the range of 98.40% to 99.89% up to 12 h. The *in vitro* release data was subjected to zero order, first order, Higuchi, and Korsmeyer-Peppas model in order to establish the drug release mechanism and kinetics of drug release from the buccal tablets. When the data was subjected to zero order and first order kinetic model, a linear relationship was observed with high 'r^2' value. This indicates that the drug release from tablet followed diffusion mechanism. In order to define a perfect model, which will repre-

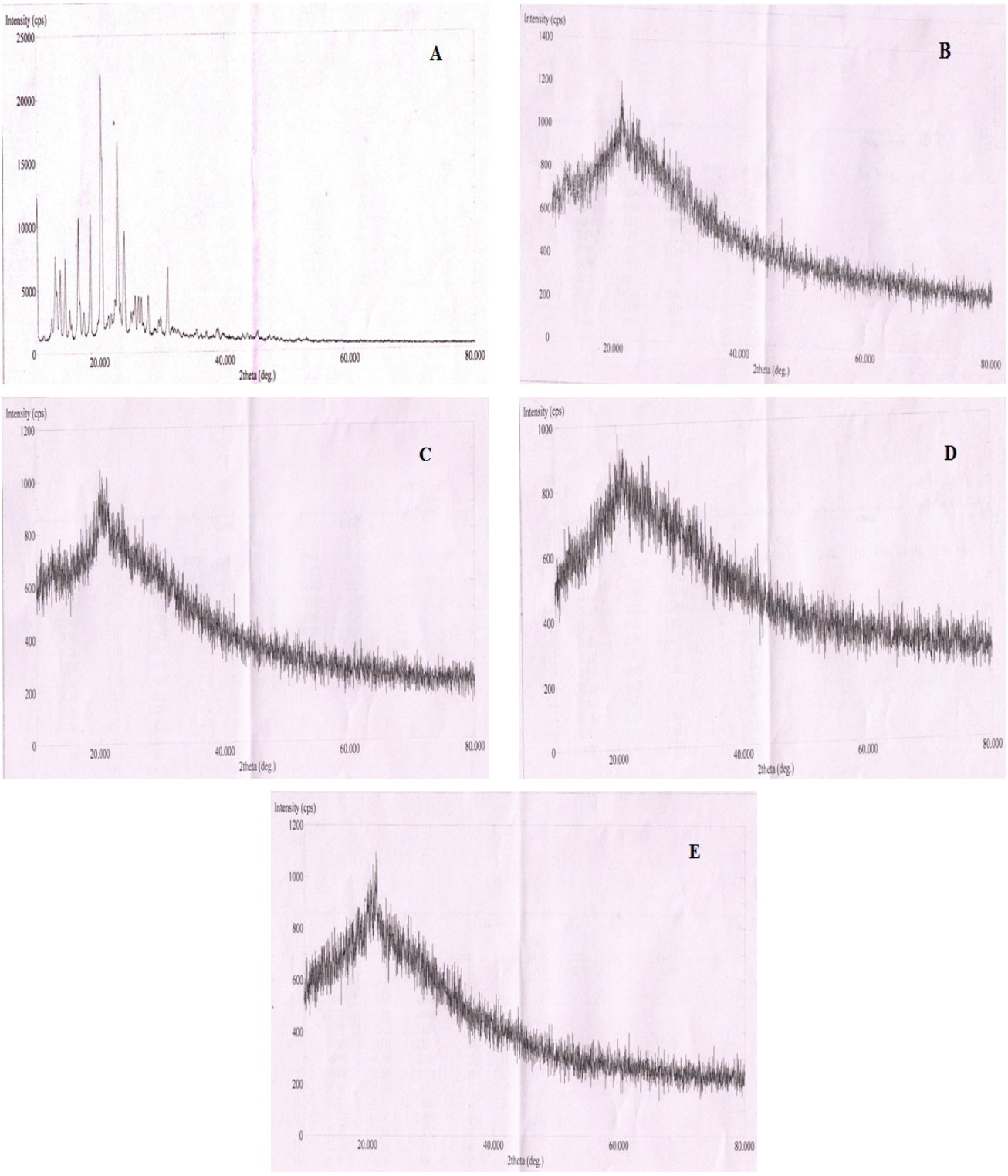

Figure 4: XRD Pattern of pure drug (A), BU1 (B), BU4 (C), BU6 (D), BU6 Dummy (E)

sent a better fit for the *in vitro* release data, Korsmeyer-Peppas model was applied which was defined exact release mechanism when more than one type of release phenomenon was observed. Good linearity with high 'r^2' value was observer with Korsmeyer-Peppas model. The value of release exponent '*n*' calculated defines the release mechanism. The value of '*n*' obtained for all the tablet formulation was >0.5 and <1.0 suggested that the drug release followed non-fickian anomalous diffusion due to the higher affinity of hydrophilic polymers towards water.

In vitro permeation study was carried out on modified Franz's diffusion cell using sheep buccal mucosa and results are shown in Figure 7. The optimized formulations BU3 and BU6 have shown 98.35 % and 93.95 %

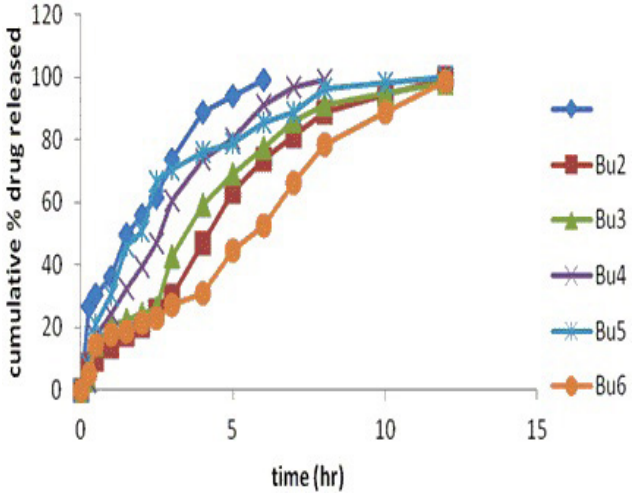

Figure 5: Cumulative percent drug release Vs time plots of formulations BU1, BU2, BU3, BU4, BU5 and BU6

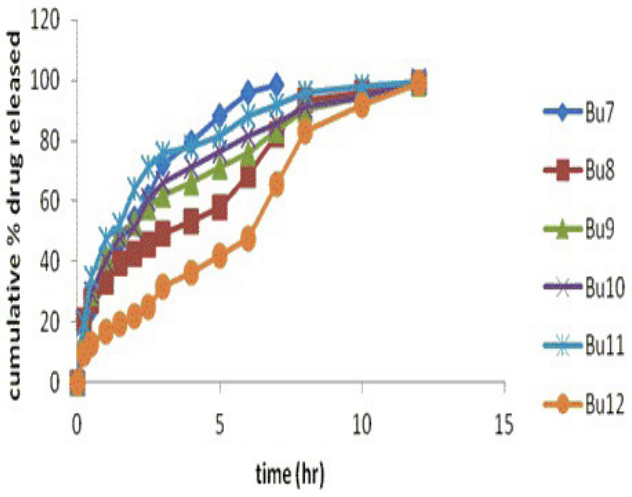

Figure 6: Cumulative percent drug release Vs time plots of formulations BU7, BU8, BU9, BU10, BU11 and BU12

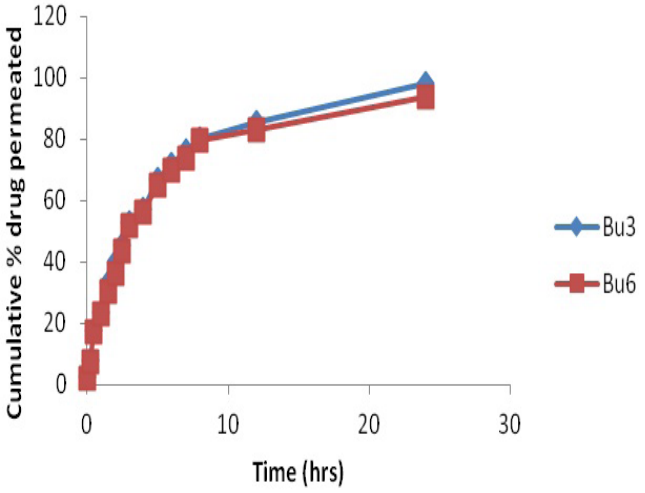

Figure 7: Cumulative percent drug permeated Vs time plots of formulations BU3 and BU6

drug permeation at the end of 24 h respectively. Based on the results of evaluation data of all the 12 formulations BU3 and BU6 were optimized because of their good bioadhesive strength and sustained release data. Further, they over ruled the drug-polymer interaction by FTIR spectroscopy, DSC and XRD.

CONCLUSION

The mucoadhesive buccal tablets of repaglinide can be prepared by wet granulation method using chitosan, HEC and guar gum along with carbopol 934P as mucoadhesive polymers in different ratios. All the prepared tablets were found to be good without capping and chipping. The prepared tablets were in acceptable range of weight variation, hardness, thickness, friability, drug content as per pharmacopoeial specifications. The increase in concentration of carbopol resulted in increased hardness of tablets. As the amount of polymer in the tablets increases, the drug release rate decreases, whereas mucoadhesive strength increases. FTIR spectroscopy and DSC studies indicated that there were no drug-excipient interactions. The tablets showed good mucoadhesive strength with high force of adhesion. *In vitro* residence test for mucoadhesion indicated good mucoadhesive property and good adhesive capacity of polymers used. The surface pH of prepared tablets suggested that prepared tablets could be used without risk of mucosal irritation. Formulations BU3 and BU6 are optimized because of their good mucoadhesive strength and ability to sustain the release of drug over 12 h period. Hence, the developed dosage forms are versatile delivery systems for repaglinide.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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