PHARMACEUTICAL AND BIOLOGICAL EVALUATIONS
June 2016; vol. 3 (Issue 3): 377-387.
www.onlinepbe.com
ISSN 2394-0859

Research Article

Formulation and evaluation of bioadhesive drug delivery system

Asif Pathan*, Asish Dev

Oriental College of Pharmacy, Sanpada, Navi Mumbai 400705, India

***For correspondence**
Asif Pathan,
Oriental College of Pharmacy, Sanpada, Navi Mumbai 400705, India.
Email: asifpathan51@gmail.com

Received: 22 April 2016
Revised: 05 May 2016
Accepted: 17 May 2016

ABSTRACT

Objective: The objective of the work is to formulate gliclazide bioadhesive tablets that will significantly improve the availability of the drug especially under the situations of prolonged use of drug and also reduce the total dosage of administered drug and consequently reduce the side effects. All these factors will ultimately lead to enhanced patient compliance and patient care.

Methods: Various natural and semi synthetic polymers were screened and they were selected on the basis of their swelling and gelling properties. The formulated batches were subjected to various evaluation parameters and optimization was done.

Results: The F7 batch was concluded to be the best batch in which Xanthan gum (70%) and HPMC K4M (30%) were taken. Stability studies of the optimized batches were conducted as per the ICH guidelines.

Conclusions: From this study it was concluded that as the thickness of tablet increases the hardness of tablet decreases which leads to increase in the swelling of the tablet and hence the increase in the drug release.

Keywords: Gliclazide, Antidiabetic drug, Bioadhesive tablets, Swelling index

Introduction

Oral route has most commonly adopted and most convenient route for the drug delivery. Oral route of administration has been received more attention in pharmaceutical field because of its flexibility in the designing of dosage form than other drug delivery design through any other routes. The oral drug delivery depends on various factors such as type of delivery system, the disease being treated, and patient, the length of the therapy and properties of the drug.[1] Recent advances in novel drug delivery system (NDDS) aims to enhance safety and efficacy of already used drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance.[2]

Controlled drug delivery

The controlled drug delivery system is intended to exercise control on drug released in the body. In other words; system attempts to regulate drug concentration within tissue or cell. The controlled or sustain delivery attempts to; sustain drug action at predetermined rate by

maintaining relatively constant, effective drug level in the body with minimization of undesirable side effects. Localized drug action can be achieved by spatial placement of sustained release system.[3]

Different approaches of controlled drug delivery

1. Sustained released.
2. Modulated released.
3. Targeted delivery.

Advantages of controlled drug delivery system[1]

1. Reduction in dosing frequency.
2. Reduced fluctuations in circulatory drug levels.
3. Avoidance of night time dosing.
4. Increased patient compliance.
5. More uniform effect.
6. Decreased side effects like reduced GI irritation.

Disadvantages of controlled drug delivery systems[1]

1. High cost,
2. Unpredictable or poor *in vitro – in vivo* correlation,
3. Dose dumping,
4. Reduced potential for dosage adjustment,
5. Increased first pass clearance,
6. Poor systemic availability in general.

Merits of controlled or sustained drug delivery systems over conventional dosage form[4]

1. Improved patient convenience and compliance due to less frequency of drug administration,
2. Reduction in adverse side effects ,
3. Increased safety margin of high potency drugs due to better control of plasma levels,
4. Reduction in health care cost due
   - To improved therapy,
   - Less frequent dosing,
   - Shorter treatment period.

Major challenge to controlled/Sustained release drug delivery system is to uphold a delivery system at exacting site for extensive time period for local and systemic bioavailability of drug also these system has disadvantage of less gastric retention time, which is a physiological limitation that leads to lower bioavailability of drug. Therefore bioadhesive dosage form has been selected which remained intact at an exacting position for prolonged period to provide a longer residence time and prolonged drug release and for targeting the delivery system at a particular location in the body.

Bioadhesive drug delivery system

The term bioadhesion refers to any bond formation between two biological surfaces or a bond between a biological and a synthetic surface. In the case of bioadhesive drug delivery systems, the term bioadhesion is typically used to describe the adhesion between polymers, either synthetic or natural, and soft tissues (i.e., gastrointestinal mucosa).[5]

Bioadhesion is an attachment of macromolecules that are synthetic or natural to mucus or surface of epithelium. This utilizes the bioadhesion property which adheres on hydration due to certain polymers. Hence, used for drug targeting at an exacting area for extensive period of time in the body. When applied to mucosal epithelium bioadhesive interactions occur primarily with the mucus layer and this phenomenon is refered to as mucoadhesion.[5]

Bioadhesive delivery system includes the following drug delivery system (DDS).[1]

a) Buccal DDS
b) Topical DDS
c) Rectal DDS
d) Ocular DDS
e) Vaginal DDS
f) Nasal DDS
g) Gastro intestinal DDS

Advantages of bioadhesive drug delivery systems[1]

a) A prolonged residence time at the site of action or absorption,
b) A localization of the drug delivery system at a given target site,
c) An increase in the drug concentration gradient due to the intestine contact of the particles with the mucosal surface,

d) A direct contact with intestinal cells, which is the step earlier to particulate absorption.

Gliclazide

Chemical Name: 1-[Hexa hydro cyclo penta [c]pyrrol-2(1H)-yl]-3-[(4-methyl phenyl) sulphonyl] urea.

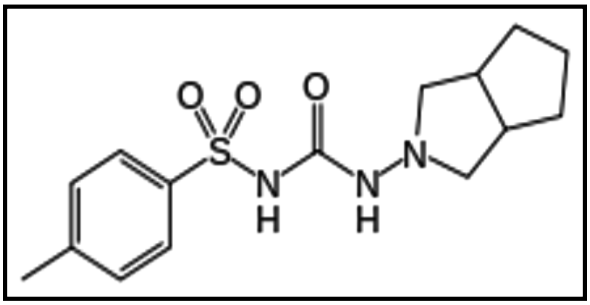

Figure 1: Gliclazide drug structure.

Materials and Methods

Materials: Gliclazide was received as a gift sample from Shandong keyuan Pharma. Talc were obtained from Research lab and magnesium stearate were obtained from Thomas Baker. HPMC K4M, Xanthan gum were obtained from Hi media, India.

All pre-compression parameters for drug and blend such as bulk density, tap density, Carr's index, Hausner's ratio and angle of repose were studied. The compressed tablets were subjected to post compression parameters such as appearance, weight variation, hardness, friability, thickness, swelling property, *in vitro* dissolution studies, content unformity test and bioadhesive strength.

Results and Discussion

Preformulation studies:[31-34]

U.V. spectrum of drug gliclazide

The solution of gliclazide in 0.1N HCL and Phosphate buffer pH 6.8 was found to exhibit maximum absorption (λ_{max}) at 224.2 nm after scanning in the range of 200-400 nm.

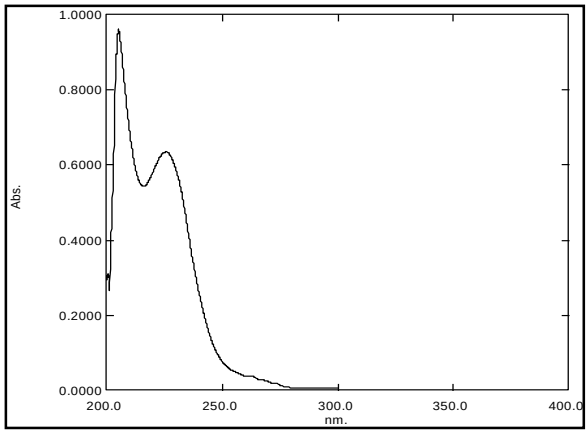

Figure 2: UV spectrum of gliclazide.

Fourier transmission infrared (FT-IR) spectroscopy

The identity of drug was confirmed by comparing IR spectrum of drug with reported spectrum of Gliclazide as shown in Figure 3.

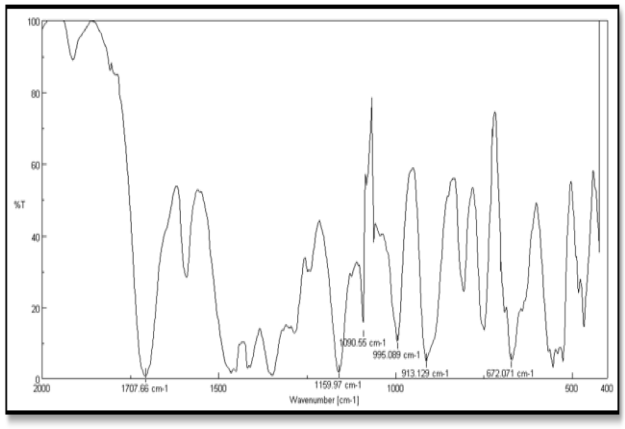

Figure 3: FTIR spectrum of drug.

Melting point

The melting point of drug was found to approximately 168˚C.

Physical properties of drug powder: The drug Gliclazide undergoes through various tests to know its physical properties. Results are shown in Table 1.

The percent compressibility of the drug was 21.2% and angle of repose was 32˚ suggesting that it can be directly compressed.

Construction of calibration curve:[35-38]

The calibration curve for Gliclazide was determined in Phosphate buffer pH 6.8 in UV spectrophotometer.

Table 1: Physical properties of drug.

Sl.No.	Test	Result
1.	Bulk density (g/ml)	0.445
2.	Tap density (g/ml)	0.566
3.	Carr's Compressibility	21.2%
4.	Hausner's ratio	1.23
5.	Angle of Repose	32˚
	Flow properties	**Passable**

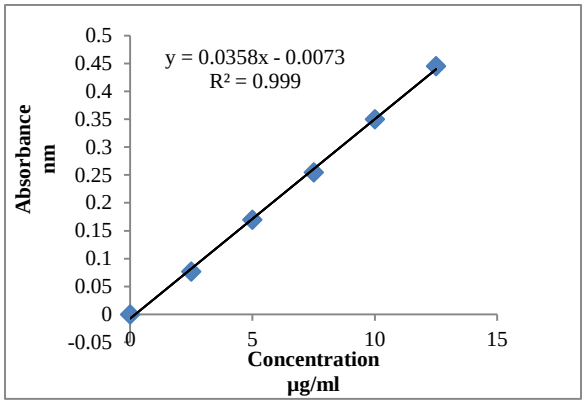

Figure 4: Calibration curve of gliclazide.

Drug excipients compatibility studies (using FT-IR spectroscopy):[39,40]

Compatibility study should be done to know if any chemical interactions exist between drug and excipients. Interpretation is done by comparing FTIR spectra of pure drug and drug-excipient mixture. Both the spectra should show that characteristic bands of drug were not altered indicates no chemical interactions between the drug and excipients used.

Screening of polymers:[1,5]

Screening of polymers was done by swelling index and gelling properties and depending on these two the shear stress measurement of polymer were studied.

Hence, from the above result of the above experiment two synthetic polymers and two natural polymers were selected and all these polymers were subjected to shear stress measurement of polymers in order to conclude the bioadhesive strength of polymers.

Shear stress measurement study was performed on polymer solution. The results were shown in Table 3.

Table 2: Swelling index and Gelling properties of polymers.

Sr.no.	Polymer	Swelling Index			Gelling		
		Water	**p^H 1.2**	**p^H 6.8**	**Water**	**p^H 1.2**	**p^H 6.8**
1	HPMC K4M	200	100	120	++	+++	+++
2	HPMC E15	300	200	450	++	+	+
3	HPMC K100	175	225	125	++	+++	+++
4	Carbopol	1220	1720	2140	+	+	++
5	Xanthan gum	400	450	450	++	++	++
6	Guar gum	333.33	300	400	+++	+++	++
7	Chitosan	66.66	100	66.66	+	+	+

Table 3: Shear stress measurement of polymer solution.

Polymer	Shear stress force		Detachment force	
	(gm)	**(N)**	**(gm)**	**(N)**
HPMC K4M	90	0.882	185	1.814
HPMC K100	27	0.264	140	1.373
Xanthan gum	110	1.079	120	1.177
Guar gum	50	0.490	110	1.079

From the above experiment it was concluded that HPMC K4M and Xanthan gum required more force as compared to HPMC K100 and Guar gum for the slide down movement or detachment of blocks. Hence, HPMC K4M as synthetic polymer and Xanthan gum as natural polymer were used for the development bioadhesive tablet.

***Pre compression parameters of blends*:**[32]

Angle of repose

Angle of Repose of powder was determined by the funnel method. Accurately weight powder blend were taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\text{Tan } \alpha = h/r$$

Bulk density and tapped density

An accurately weighed quantity of the blend (W), was carefully poured into the graduated cylinder and the volume (V_0) was measured. Then the graduated cylinder was tapped and volume (V_t) was measured which was tapped volume. The bulk density and tapped density were calculated by using the following formulas.

$$\text{Bulk density} = W/V_0$$
$$\text{Tapped density} = W/V_t$$

Compressibility index (CI)/ Carr's index

It was obtained from bulk and tapped densities. It was calculated by using the following formula.

$$CI = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped density}} X\ 100$$

Hausner's ratio

Hausner's ratio is a number that is correlated to the flowability of a powder. It is measured by ratio of tapped density to bulk density.

$$\text{Hausner's ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Table 4: Pre compression parameters of blends.

S. no	Test	F1,F2,F3	F4,F5,F6	F7,F8,F9
1.	Bulk density (gm/ml)	0.58	0.56	0.46
2.	Tap density (gm/ml)	0.71	0.68	0.55
3.	Carr's Compressibility	18.30%	17.64%	16.36%
4.	Hausner's ratio	1.22	1.21	1.19
5.	Angle of Repose	37.87˚	36.38˚	33.02˚
Flow properties		**Passable**	**Passable**	**Passable**

Method of preparation

The initial screening and selection of polymers were done based on their swelling and gelling properties. From the initial observation two polymers were selected for further optimization of formulation batches, they are HPMC K4M and Xanthan gum. Different concentrations of each polymer were also further explored for their role in bioadhesiveness and drug release along with their swelling capacity.

Preparation of bioadhesive tablets

Tablets containing 30 mg of Gliclazide were prepared by direct compression technique and various formulae used in the study are shown in the Table 1. Drug, polymers and other excipients were weighed accurately. The active ingredient Gliclazide, all polymers and other excipients except lubricants get sifted through sieve 40#. They were properly mixed. The blend was evaluated for pre compression parameters. Then the blend was lubricated by magnesium stearate and talc. The prepared blend was compressed into tablets by using 9 mm punch using 8 station tablet punching machine. The tablets were evaluated for appearance, weight variation, hardness, friability, thickness, swelling index and *in vitro* drug release.

All tablets were stored in airtight containers at room temperature for further study.

Post compression evaluation of bioadhesive gliclazide tablets:[31,42]

Appearance

Pale white in color.

Weight variation test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance United Weigh Scale, and the test was performed according to the official method.

Content uniformity test:[48]

Assay of drug content was performed in triplicate for each gliclazide tablet formulation. An amount of powder equivalent to 30 mg of gliclazide was weighed and transferred to a 50 ml volumetric flask. Methanol and pH 6.8 phosphate buffer solution was used to dissolve the drug under sonication for 15 minutes. Then samples were filtered through a 0.45 µm diameter membrane. Filtered solutions were suitably diluted with pH 6.8 phosphate buffer solution and drug content of the diluted solutions were measured using a UV spectrometer at a wavelength of 224.2 nm.

The drug content was calculated as:

% Drug Content = (Analysed value / Theorotical Value) × 100

Hardness

Hardness of the tablets was determined using a digital tablet hardness tester Monsanto hardness tester.

A tablet hardness of about 2-4 kg/cm^2 is considered adequate for mechanical stability.

Friability

Friability test of tablets should be done to ensure the tablets are stable to abrasion or not. Friability is tested using Roche friabilator. 20 tablets are weighed and placed in the plastic drum attached to the machine rotated at 25 rpm for 100 revolutions. Then tablets are cleaned with a cloth and weighed again. Percentage friability is calculated as follows:

% Friability = $(W_0-W)/ W_0*100$
Where, W_0 = Initial weight of 20 tablets
W = Weight after 100 revolutions

The weight loss should not be more than 1% w/w.

Thickness

Thickness of the tablets was determined using a digital vernier caliper AEROSPACE.

Table 5: Formulation batches from F1 to F9.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Gliclazide (mg)	30	30	30	30	30	30	30	30	30
HPMC K4M (%)	70	70	70	50	50	50	30	30	30
Xanthan gum (%)	30	30	30	50	50	50	70	70	70
Talc (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium stearate (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total (mg)	200	200	200	200	200	200	200	200	200

Table 6: Physical properties of tablets.

Batch No.	Appearance	Weight variation (mg)	Hardness Kg/cm^2	Friability (%)	Thickness (mm)
F1	+++	199±0.07	4±0.01	0.20	2.70±0.01
F2	+++	200±0.01	4±0.01	0.25	2.78±0.01
F3	+++	201±0.05	4±0.01	0.32	2.88±0.01
F4	+++	200±0.07	3.5±0.05	0.20	2.70±0.01
F5	+++	199±0.02	3.5±0.05	0.29	2.78±0.01
F6	+++	201±0.06	3.4±0.01	0.39	2.88±0.01
F7	+++	200±0.03	3.2±0.01	0.76	2.70±0.01
F8	++	201±0.02	2±0.03	0.78	2.78±0.01
F9	++	201±0.07	2±0.03	0.81	2.88±0.01

+ Poor, ++ Acceptable, +++ Good

Table 7: Swelling index of tablets.

Time (Hrs)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)	F9 (%)
1	138.69	138.80	140.79	120	123.61	123	146	152.47	178.60
2	158.79	159.20	161.19	141.5	143.71	144	181	189.60	208.45
3	178.89	178.10	180.09	190	193.96	194.5	241	241.58	288.05
4	314.57	312.93	315.42	225	229.14	229	291	291.08	317.91
5	339.69	337.81	340.29	246.5	249.24	249.5	336	336.63	357.71
6	369.84	367.66	370.14	257	259.29	260	356	362.87	392.53
7	420.10	417.91	419.90	275	279.39	280	411	419.80	442.28
8	425.12	421.89	425.37	282.5	284.42	282.5	426	435.64	452.23
9	430.15	427.36	429.35	290.5	294.47	295	451	454.45	462.18
10	435.17	432.33	433.83	305	309.54	310	461	466.83	477.11

Table 8: Dissolution studies of all above batches shows % cumulative drug release.

Time (hrs.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	11.376	12.969	12.21	12.11	13.5	14.55	15.14	13.5	13.23
2	16.668	13.587	14.94	37.58	34.93	37.85	41.92	37.32	38.58
3	50.013	26.12	27.21	48.42	50.55	53.47	61.14	57.17	70.84
4	55.836	40.761	47.64	51.06	51.08	53.99	68.13	73.27	75.70
5	56.106	56.376	51.61	54.52	58.23	61.41	68.42	80.069	83.95
6	63.252	62.995	71.99	56.38	59.02	65.11	71.62	83.46	88.80
7	68.814	83.52	83.28	61.11	64.84	68.81	77.15	89.72	97.53
8	69.588	97.752	98.25	62.20	65.37	66.97	79.77	97.54	-
9	76.491	-	-	66.17	66.17	70.14	86.18	-	-
10	80.578	-	-	69.88	69.61	74.38	89.95	-	-

In vitro dissolution studies:[43-47]

USP Dissolution apparatus of type 2 (paddle) was used for *in vitro* drug release study. 100 0.1 N HCL and Phosphate buffer pH 6.8 of 900 ml used as dissolution medium. Temperature maintained at 37 ± 0.5^{0}C and RPM of 100. A suitable volume of sample was removed at regular intervals of 1,2,3,4,5,6,7,8,9,10 hrs. Every time the sample withdrawn was replaced

by fresh dissolution medium maintained at the same temperature. The sample removed was filtered, diluted and analyzed at 224.2 nm using UV-Vis spectrophotometer.

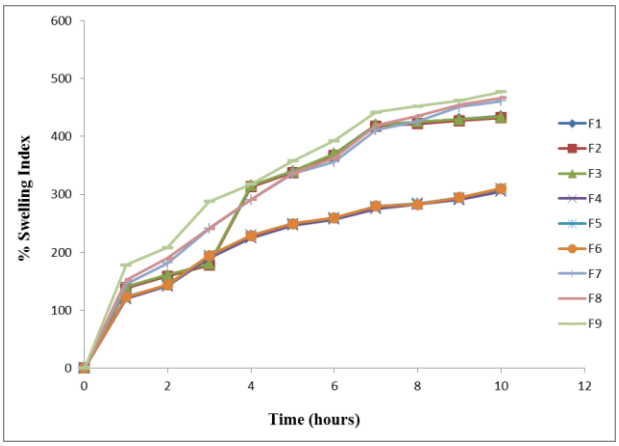

Figure 5: Swelling Index of different formulations (F1-F9).

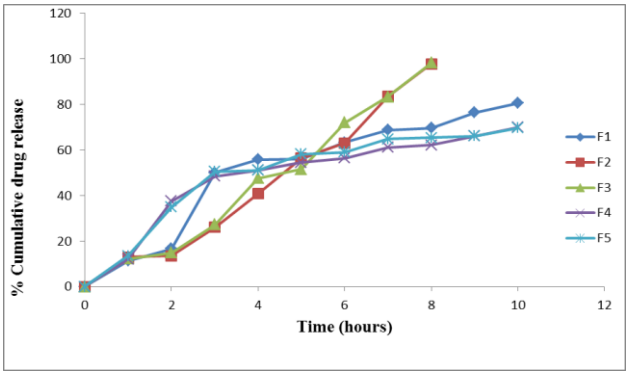

Figure 6: *In vitro* drug release profile of batches (F1-F5).

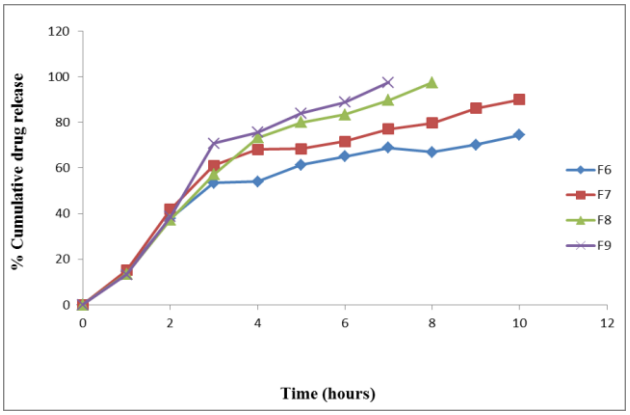

Fig 7: *In vitro* drug release profile of batches (F6-F9).

Bioadhesive strength of a tablet: Bioadhesive strength of a tablet was determined in the acidic and basic media the results are as follows.

Table 9: Bioadhesive strength of a tablet in acidic media.

Batch no.	Bioadhesive strength (gm)	Bioadhesive force (N)
F1	36	0.353
F2	34	0.333
F3	28.5	0.279
F4	37	0.362
F5	32.3	0.316
F6	29	0.284
F7	56.6	0.555
F8	52	0.510
F9	47	0.461

Table 10: Bioadhesive strength of a tablet in basic media.

Batch no.	Bioadhesive strength (gm)	Bioadhesive force (N)
F1	28.5	0.279
F2	25	0.245
F3	21.5	0.210
F4	30	0.294
F5	26.2	0.257
F6	24	0.235
F7	42.5	0.416
F8	39.6	0.388
F9	35	0.343

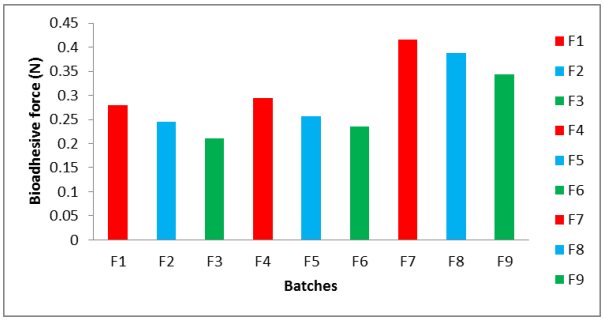

Figure 8: Bioadhesive strength of a tablet in acidic media.

From the above result it was reveal that batch F7 tablet required higher force to detached from the gastric mucosa.

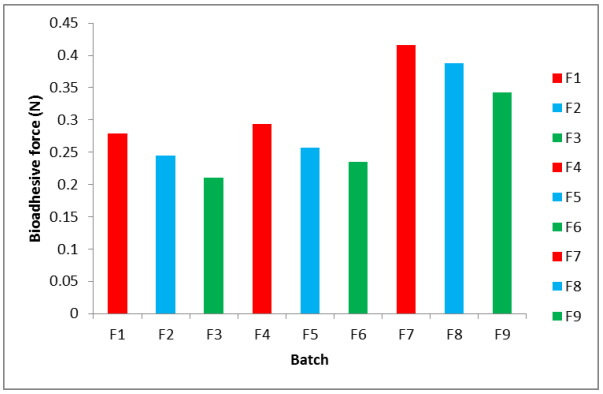

Figure 9: Bioadhesive strength of a tablet in basic media.

From the above result it was reveal that batch F7 tablet required higher force to detached from the intestinal mucosa.

Stability studies:[49]

The optimized batch is subjected to accelerated stability studies at 40˚C ± 2˚C/75 % RH ± 5 % RH for duration of three months to investigate stability of formulation in terms of physical and chemical changes. Stability study of optimized F7 batch indicates no significant change in physical parameters. The *in vitro* dissolution studies, content uniformity test and bioadhesive strength of optimized batch F7 shows satisfactory results.

Conclusions

Bioadhesive tablet of Gliclazide were prepared by Direct Compression method using polymer such as HPMC K4M and Xanthan Gum, other excipients such as Magnesium stearate and talc. All pre-compression parameters for drug and blend such as bulk density, tap density, Carr's index, Hausner's ratio and angle of repose were studied. The compressed tablets were subjected to post compression parameters such as appearance, weight variation, hardness, friability, thickness, swelling property, *in vitro* dissolution studies, content uniformity test and bioadhesive strength.

In vitro dissolution studies of nine batches concluded that the batch F2, F3 and F8 tablets completely disintegrated at 8 hour and batch F9 completely disintegrated at 7 h so these batches were rejected.

Amongst the other batches F7 batch was selected as an optimized batch because the Pre and Post compression parameters results are satisfactory. The F7 batch showed best result as the percent cumulative drug release of F7 is 89.95% at 10 h and also % swelling index is about 461 at 10 h. The tablet does not swell too much, which results in controlled release of drug and also shows good bioadhesive strength in both acidic and basic media.

From this study it was concluded that as the thickness of tablet increases the hardness of tablet decreases which leads to increase in the swelling of the tablet and hence the increase in the drug release.

Stability study of optimized F7 batch indicates no significant change in physical parameters. The *in vitro* dissolution studies, content uniformity test and bioadhesive strength of optimized batch F7 shows satisfactory results.

Funding: No funding sources
Conflict of interest: None declared

References

1. Robinson JR, Lee VH. Controlled drug delivery: fundamentals and applications, 2nd ed.; Marcel Dekker Inc; Taylor and Francis: New York; 1987: 3 - 49.
2. Mubashshir MM, Dev A. Indian Journal of Pharmaceutical and Biological Research. 2015;3(1):18-23.
3. Mathiowitz E, Chickering DE, Lehr CM. Defination Mechanism and Theories of bioadhesion Bioadhesive Drug Delivery Systems, Marcel Dekker, Eastern Hemisphere Dustribution: USA; 2010: 1-22.
4. Jain NK. Progress in Controlled and Novel Drug Delivery Systems. CBS. Publisher. Indian binding house press: Noida; 2010: 79–80.
5. Jain NK. Controlled and Novel Drug Delivery Systems. CBS Publisher: Delhi; 1997: 356.

6. Saraswathi B, Balaji A, Umashankar MS. Polymers in mucoadhesive drug delivery system-latest updates. Int J Pharm Sci. 2013;423–30.
7. Singh S, Govind M, Bothara SB. A Review on in vitro - in vivo Mucoadhesive Strength Assessment. Pharma Tech Medica. 2013;221-7.
8. Tangri P, Madhav NVS. Oral mucoadhesive drug delivery systems: A Review. Int J Biopharm. 2011;2:36–46.
9. Khurana S, Madhav NVS, Pranshu T. Mucoadhesive drug delivery: Mechanism and method of evaluation: A Review. Int J Pharm Biosci. 2011;2:458–64.
10. Hiremath SR, Murthy SN. Controlled Drug Delivery Systems, Text book of Industrial Pharmacy, Orient Longman private, India; 2008: 5–17.
11. Phanindra B, Moorthy BK, Muthukumaran M. Recent advances in mucoadhesive /bioadhesive drug delivery system: A review. Int J Pharm Med Bio Sci. 2013;2:68–73.
12. Yadav VK, Gupta AB, Kumar R, Yadav JS, Kumar B. Mucoadhesive Polymers: Means of Improving the Mucoadhesive properties of drug delivery system. J Chem Pharm Res. 2010;5:418–32.
13. Cavalho FC, Bruschi ML, Evangelista RC. Mucoadhesive drug delivery systems: A Review. Int J Pharm Sci. 2010;46:1–17.
14. Martin A, Swarbrick J, Cammarata A. Physical Pharmacy, 6th ed, Varghese Publishing house: Bombay; 1991: 592–506.
15. Lee JW, Park JH, Robinson JR. Bioadhesive based dosage forms: The next generation. J Pharm Sci. 2000;89:850–66.
16. Park JH, Robinson JR. Bioadhesive polymers as platforms for oral controlled drug delivery methods to study bioadhesion. Int J Pharm. 1984;19:107.
17. Sachan NK, Bhattacharya A. Basics and Therapeutic potentials of oral mucoadhesive microparticulate drug delivery systems. Int J Pharm Cl Res. 2009;10–4.
18. Diabetes mellitus. https://en.wikipedia.org/wiki/Diabetes_mellitus. Accessed 14 December 2014.
19. Dandiya PC, Kulkarni SK. Introduction to pharmacology, 6th ed, Vallabh Prakashan, Chandigarh; 2002: 352 – 353.
20. Bjelakovi G, Nagorni A, Stamenkovi I, Benedeto-Stojanov D, Bjelakovi M, Petrovi B, et al. Diabetes mellitus and digestive disorders: Review article. Acta Fac Med. 2005;1:43–50.
21. Gliclazide: https://en.wikipedia.org/wiki/Gliclazide. Accessed 03 October 2014.
22. Jhon HB, Jhon MB. Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry. Quebecor World Press: Philadelphia; 2004: 670.
23. Sarkar A, Tiwari A, Bhasin PS, Mitra M. Pharmacological and pharmaceutical profile of gliclazide: A Review. J App Pharm Sci. 2011;1:11–9.
24. British Pharmacopoeia, 2009, Volume 1, p 937.
25. Raymond C, Paul JS, Marian EQ. A Handbook of Pharmaceutical Excipients, 4th ed. Pharmaceutical press, Lambeth High Street, London; 5; pp 297 – 299, pp 354 – 356, pp 641 – 643, pp 691 – 692.
26. HPMC: https://en.wikipedia.org/wiki/Hypromellose. Acessed 7 May 2015.
27. Xanthan gum: https://en.wikipedia.org/wiki/Xanthan_gum. Accessed 7 May 2015.
28. Magnesium stearate: https://en.wikipedia.org/wiki/Magnesium_stearate. Accessed 7 May 2015.
29. Talc: https://en.wikipedia.org/?title=Talc Accessed 7 May 2015.
30. Lachman L, Lieberman HA, Kanig JL. The theory and practice of industrial pharmacy. Varghese Publishing house: Bombay; 2009: 171 – 195
31. Aulton ME. The Design and Manufacture of Medicines, Livingston Publisher: Elsevier Science 3rd ed.; 2007: 355 – 357.
32. Aulton ME. Pharmaceutics: The science of dosage form design. Livingston Publisher: Elsevier Science; 2002: 114–115, 289–315, 661.
33. Adeyeye MC, Brittain HG. Preformulation in solid dosage form development, Informa health care: USA; 2008;178:1–15.
34. Beckett AH, Stenlake JB. Practical Pharmaceutical Chemistry, CBS publishers, part two, 4th ed.; 275 – 281.

35. Jamadar SA, Mulye SP, Karekar PS, Pore YV, Burade KB. Development and validation of UV spectrophotometric method for the determination of gliclazide in tablet dosage form. Der Pharma Chemica. 2011;3:338–43.
36. Dhabale PN, Seervi CR. Simultaneous UV spectrophotometric method for estimation of gliclazide and Metformin hydrochloride in tablet dosage form. Int J Chemtech Res. 2010;2:813–7.
37. Revathi R, Saravanan VS, Raj MP. Ethiraj T. Ganesan V., Spectrometric estimation of gliclazide in bulk and pharmaceutical dosage forms. Int Res J Pharm. 2010;1:277–81.
38. Pavia DL, Lampman GM, Kriz GS. Introduction to Spectroscopy; Malloy Lithographing press: USA; p. 13.
39. Chatwal RG, Shyam KA. Instruments Methods of chemical analysis, Himalaya publishing house: Mumbai; 2008: 2.55.
40. Shaikh DM, Shende MA, Shaikh AM. Formulation development and evaluation of Gastro Retentive Mucoadhesive Tablets using synthetic polymers. Int J Res Pharm Sci Bio Sci. 2013: 1265.
41. The Indian Pharmacopoeia Commission, Ministry of Health and Family Welfare, Govt. of India, Ghaziabad, Indian Pharmacopoeia, 2010, Volume 1: 192–193.
42. Badgujar P, Shaikh T. Development of dissolution media for marketed gliclazide modified release tablets. Int J Pharm Sci. 2013;4:352–62.
43. United States Pharmacopoeia 32 and National formulary 27, volume 1, 2009, p. 264-269.
44. British Pharmacopoeia, 2009, Volume 4 Appendix XII B A 295 – 299.
45. Lakka NS, Goswami N. Solubility and dissolution profile studies of gliclazide in pharmaceutical formulations by RP – HPLC. Int Res J Pharm. 2012;3:126–9.
46. Demirturk E, Oner L. Solubility and dissolution properties of gliclazide. J Pharm Sci. 2004;29:21-5.
47. Nguyen C, Christensen JM, Nguyen T. Application of D-Optimal Study Design with Contour Surface Response for Designing Sustained Release Gliclazide Matrix Tablets. Pharmacology & Pharmacy. 2014;5:620–35.
48. U.S. Department of Health and Human Services FDA, Guidance for Industry Q1A(R2) Stability Testing Of New Drug Substances and Products, November 2003 ICH Revision 2 pp 5.
49. Cartensen J. ICH Guidelines. In: Drug Stability Principles and Practices, 2nd ed., New York, Marcel Dekker Inc.; 1995: 541–546.