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PHYSICOCHEMICAL INVESTIGATION OF TOLBUTAMIDE TO CHECK ITS SUITABILITY FOR MAKING SUSTAINED-RELEASE FLOATING MATRIX BEADS AND TABLETS

Narendra Tomer[1], Krishan Pal[1], Anurag[2], Alok Sharma[2]

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Abstract

Gastro retentive drug delivery systems are prepared to enhance stay duration in the stomach for a prolonged period. These systems are useful for the drugs meant for localized delivery into the stomach or are highly absorbed and poorly absorbed from the intestine because of alkaline pH. These techniques help increase the solubility of the drug before gastric emptying and cause enhanced bioavailability. Therefore, we aimed to make gastroretentive floating matrix beads and tablets of the antidiabetic drug Tolbutamide because of the different advantages of gastroretentive drug administration. Floating matrix beads and tablets are dosage forms that are easy to make and can release the medicine for a long time in the stomach. However, the physicochemical properties of tolbutamide need to be investigated to determine whether they support forming gastroretentive floating matrix beads and tablets. Being freely soluble in water, it can be considered a good candidate for gastroretentive dosage forms. It doesn't show any compatibility issues with the polymer used; hence considered good on the safety issue. In conclusion, Tolbutamide, if used as gastroretentive drug delivery system, may work efficiently and will be able to improve the therapeutic, allowing blood glucose levels to be maintained more effectively.

Keywords: gastroretentive drug delivery, Physicochemical properties, Tolbutamide, Antidiabetic, Floating matrix tablet.

[1]Shri Venkateshwara University, Rajabpur, NH-24, Venkateshwara Nagar, Gajraula, Uttar Pradesh-244236, India

[2]Meerut Institute of Engineering and Technology, N.H. 58, Delhi-Roorkee Highway, Baghpat Road Bypass Crossing, Meerut, Uttar Pradesh- - 250005, India

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Introduction

The oral route of medication administration is the most common way to take pharmaceuticals that have a systemic impact. Oral Drug Delivery Systems (D.D.S.) account for over half of all drug delivery systems on the market. These systems offer additional benefits owing to patient acceptability and simplicity of administration.[1] Most pharmaceutical experts are now working on building an ideal D.D.S. with the benefit of a single dose for the length of therapy and delivering the active medicine directly to the specified spot. Controlled release methods get close to being perfect. This approach entails the predictability and repeatability of drug release, drug concentration in the target tissue, and drug therapeutic effect optimization by managing drug discharge in the body with a lesser and less frequent dose.[2,3]

One of the most challenging aspects of constructing a controlled release system for more excellent absorption and bioavailability is the inability to restrict the dose form in the targeted region of the GIT.[4]

Gastro-retentive medication delivery systems can stay in the stomach for a prolonged period. Medications that are degraded in the intestine or drugs like antacids or some antibiotics, as well as enzymes that should function locally in the stomach, require such holding devices. Suppose a medicine is poorly soluble in the intestine due to an alkaline pH. In that case, its retention in the gastric area may enhance solubility before emptying the stomach, resulting in higher bioavailability. Such technologies are better for enhancing G.I. absorption of medications with limited absorption windows and controlling pharmaceutical release with site-specific absorption limitations. Retaining the drug delivery system in the stomach extends the total G.I. transit time, improving bioavailability for particular medicines.[2,4]

Several strategies can be used to ensure regulated gastric retention of solid dosage forms, each with its benefits and drawbacks. A novel emulsion gelation approach is applied to make floating gel beads, best suited for a highly water-soluble medication employing sodium alginate as a polymer. This polymer is used to thicken and gel products. It also minimizes interfacial tension between the oil and water phases and effectively creates emulsion. The beads float for several hours and provide a consistent release pattern.[4,5]

Alginate is a linear copolymer made up of D-mannuronic acid and L-guluronic acid. They appear in alginate molecules as M-block or G-block areas made up entirely of one unit or as a region in which the monomer approximates an alternating sequence. Calcium ions or multivalent cations can cause sodium alginate to form stiff gels.[6,7,8]

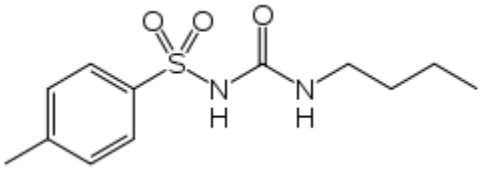
Anti-diabetic medications are used to treat diabetes mellitus by reducing blood glucose levels. All oral hypoglycemic drugs and oral antihyperglycemic medications, with the exemption of insulin, exenatide, and pramlintide, are delivered orally and are hence stated to as oral hypoglycemic agents or oral antihyperglycemic agents. Anti-diabetic medications are divided into numerous groups, and their usage is dogged by the type of diabetes, the person's age and condition, and other considerations. Diabetes mellitus type 1 is an insulin-deficiency disorder. Type I diabetes necessitates the administration of insulin, which must be injected or inhaled. Diabetes mellitus type 2 is a condition in which cells become resistant to insulin. We aimed to make gastro-retentive floating matrix beads and tablets of the antidiabetic medication Tolbutamide because of the different advantages of gastro-retentive drug administration. Floating matrix beads and tablets are a dose form that is easy to make and has the advantage of releasing the medicine for a long time in the stomach.[9] This dosage form would improve the

therapeutic action of antidiabetic medications, allowing blood glucose levels to be maintained more effectively. The physicochemical investigations of the gastro-retentive floating matrix beads and tablets of the drug Tolbutamide are detailed in this research study.

Material and Methods

Drug: Tolbutamide

Structure:



IUPAC Name: *N*-[(butylamino)carbonyl]-4-methylbenzenesulfonamide

Fig. 1 Structural formula of drug Tolbutamide

Tolbutamide is a sulfonylurea oral hypoglycemic medication that is a first-generation potassium channel blocker. If diet alone is not beneficial in treating type 2 diabetes, this medication may be taken. Tolbutamide causes the pancreas to secrete more insulin. This medicine is ineffective in treating type I diabetes because it requires the pancreas to produce insulin to operate. Because of its fast metabolism, it has a brief effect duration and is safe to use in elderly diabetics.

Identification of Drug

Identification of obtained drug is one of the preliminary tests to be done before formulation creation to validate and confirm the purity of procured drug sample. As a compendia test, an identification test is provided to assist in establishing the identity of goods as purported. The appearance, solubility, melting point, and Fourier-transform infrared (FT-IR) spectroscopy were used to identify the medication in this study.

Description of Drug

The physical qualities of medications, such as condition, colour, odour, and taste, were investigated and compared to the drug's purported description.

Melting Point

One of the identification tests for organic compounds is the melting point. The capillary melting point technique was used to determine the drug's melting point. The medicine was placed in a capillary tube with a thin wall and one end that was sealed. The capillary was then placed in a melting point device, which was gradually raised in temperature—the temperature range where the medication melts were visually seen.

Solubility

As part of the purity test, solubility tests were carried out. The solubility of the medicine was determined by placing 10 mg of the drug in a test tube and gradually adding 0.1 ml of solvent. The solvent was continued to be added until the sample was dissolved. The solubility of the medication powder was measured in terms of the solvent required for solubilization, and the results were compared to previously published values.

Characterization of Drugs by FTIR

The Fourier transform infrared (FT-IR) method is used to characterize the solid state of medicinal substances. The substance was identified using an (FT-IR) spectroscopic approach and an Alpha Bruker FTIR spectrophotometer. The medication was combined with the appropriate amount of KBr and pelletized using a KBr press at 20 pressure for 10 minutes. The disc was then put in a sample chamber and scanned at a resolution of 4000 to 400 cm^{-1} in transmission mode. The

drug's infrared spectrum was so acquired and compared to reference spectra.

Analytical Methods

Analytical methodologies are necessary for drug content estimates at various phases of research. For accurate, precise, and easy drug analysis throughout the investigation of physicochemical properties, optimization, *in vitro*, and *in vivo* assessments, appropriate analytical procedures were established.

Development of UV Spectrophotometric Method for Determination of Tolbutamide

A UV spectrophotometric technique for estimating tolbutamide in Methanol and 0.1 N HCl has been published in the literature. An established test technique was used to estimate Tolbutamide in the tablet dosage form. The Tolbutamide calibration curve was generated in 0.1 N HCl at 230 nm.

Calibration Curve of Tolbutamide in 0.1 N HCl as a Solvent

In vitro release experiments employed the Tolbutamide calibration curve in 0.1 N HCl to determine drug release.

Preparation of stock solution:

Tolbutamide was weighed accurately and placed into a 100 mL volumetric flask. The drug was mixed and diluted to the desired concentration using 0.1 N HCl, yielding a 1000 g/ml solution. To make a stock solution with a 100 µg/ml concentration, an aliquot of 10 ml from the aforesaid solution was taken and diluted up to 100 ml with 0.1 N HCl.

Preparation of solutions to obtain a calibration curve

Appropriate aliquots of Tolbutamide stock solution (0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, and 5 ml) were accurately extracted and diluted up to the mark with 0.1 N HCl to achieve a final concentration of the solution in the series of 5-50 µg/ml. A drug-free solution was employed as a blank for spectroscopic measurements. A 10 µg/ml solution was scanned at 200-400 nm wavelength using a double beam spectrophotometer to determine the λmax. The absorbance of the calibration plot's produced solutions was measured at Tolbutamide's λmax. The absorbance measuring process was repeated three times. To create a calibration curve, the mean value of the absorbance (n=3) was plotted versus concentration.

Drug Excipient Compatibility Study

In every formulation, drug-polymer interaction is always a potential. Research using Fourier-transform infrared spectroscopy (FTIR) was conducted to see whether there was any connection. The FTIR scans of pure drug (Tolbutamide), polymers (HPMC K15M and kappa carrageenan), and drug-polymer mixtures were performed. IR grade KBr combined the pure drug, polymer, and physical mixture separately. The combination was then scanned across a 4000 to 400 cm^{-1} wavenumber range.[10]

Results and Discussion

Identification of Drug

Identification of Drug by Description, Solubility, and Melting Point

Table 1 shows the identification of Tolbutamide based on physical inspection and melting point measurements.

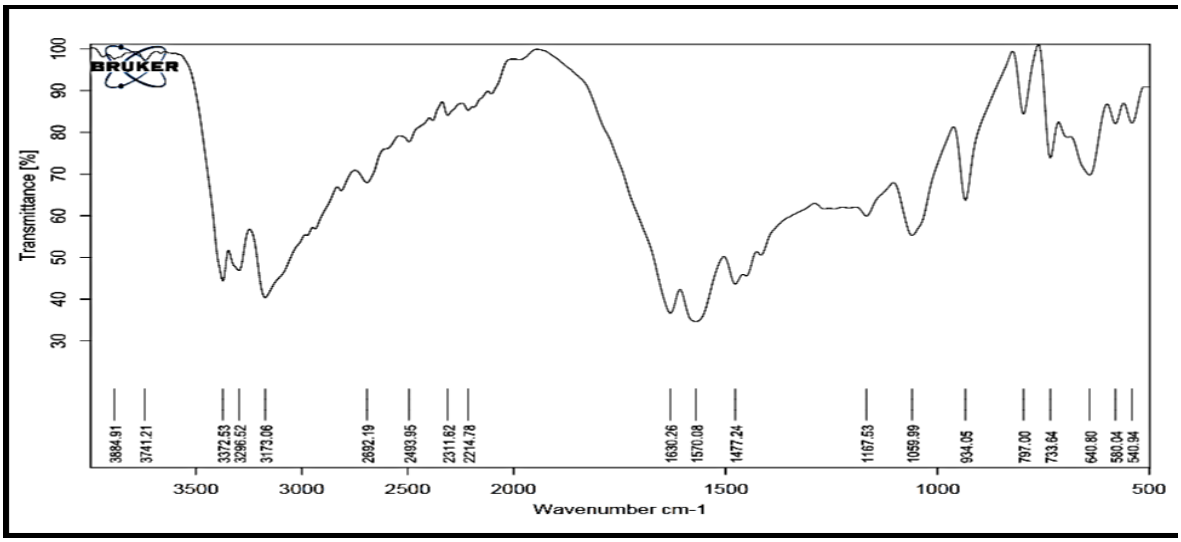
Table 1 Physical parameters of the drug Tolbutamide

Sr. No.	Test	Specification	Observation	Inference
1	State	Solid Crystalline	Solid Crystalline	Complies
2	Colour	White	White	Complies
3	Taste	Bitter	Not Performed	Complies
4	Melting Point	222-226°C	224-226°C	Complies
5	Solubility	Freely soluble in water. Slightly soluble in ethanol.	Freely soluble in water. Slightly soluble in ethanol.	Complies

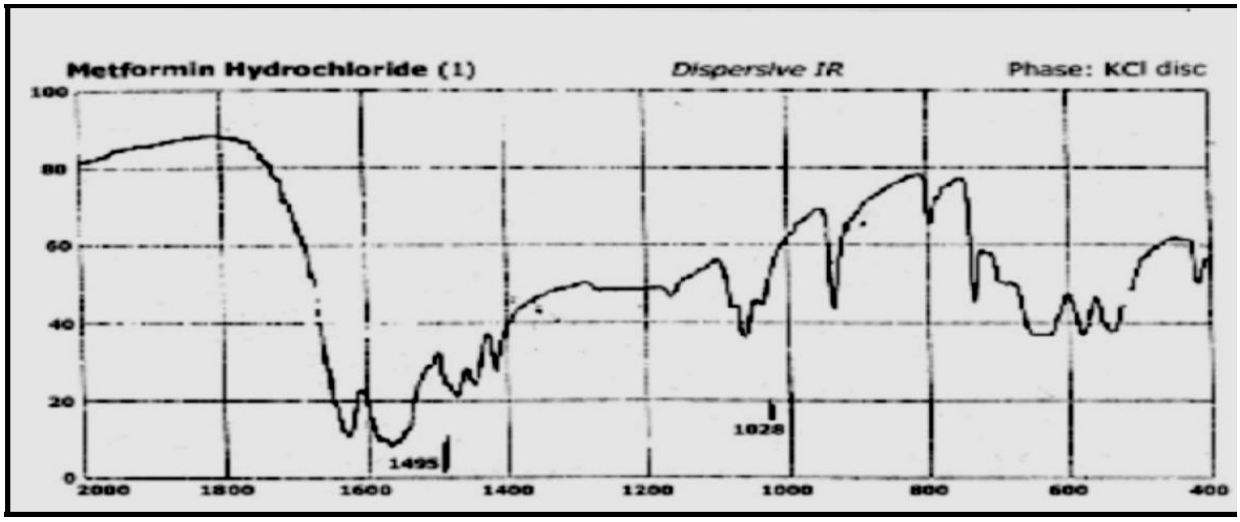
The acquired value of the medication's melting point was determined to be similar to the declared value, demonstrating that the drug samples received meet the described parameters. Any impurity will induce a change in the melting point of a pharmacological substance if it is present.

Characterization of the drug by FTIR

FTIR spectra of Tolbutamide were produced and compared to reference IR spectra to identify and confirm several functional groups. Figure 2 shows the observed and reported spectra of Tolbutamide. For interpretation, several stretching and bending peaks were identified in the spectra depicted in Table 2. It was found to be very similar to the standard spectra published elsewhere. Two 2º amine and s=o groups were identified as the major functional group of this drug.



(a)



(b)

FIGURE 2 (a) Observed FT-IR Spectra of Tolbutamide **(b)** Reference FT-IR Spectra of Tolbutamide

Table 2: Interpretation of FT-IR spectra of the drug Tolbutamide

Peak Assignment	**Wave Number (cm^{-1})**	
	Reported Data	**Observed Data**
N-H Stretching	3372	3372
Asymmetric N-H Stretching	3300	3296
Symmetric N-H Stretching	3176	3173
Asymmetric N-H Deformation	1566	1570
N-H Deformation	1626	1630

Analytical Methods

For assessing drug content, drug release, entrapment efficiency (if applicable), and *in vivo* drug release throughout the formulation and optimization stages, precise, simple, and rapid analytical procedures are required.

Development of UV Spectrophotometric Method for Determination of Tolbutamide

Simple, accurate, rapid, and precise ultraviolet (UV) spectrophotometric methods are reported in the literature for the estimation of Tolbutamide in bulk, dosage form and stability samples. Hence, calibration curves of Tolbutamide were prepared in methanol and 0.1 N HCl to determine the content and in vitro release.

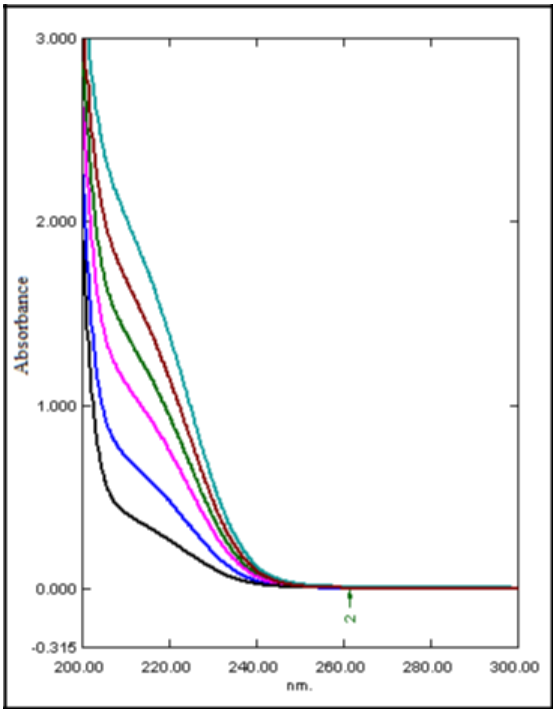
Standard Calibration Curve of Tolbutamide in 0.1 N HCl by UV Spectrophotometer

The calibration curve of Tolbutamide was prepared in 0.1 N HCl at 230 nm in the concentration series of 5-50 µg/ml. The overlay spectra and calibration curves are depicted in Fig. 3. Data obtained for the calibration is shown in Table 3. The regression analysis was performed and a correlation coefficient of 0.999 was obtained for the calibration curve.

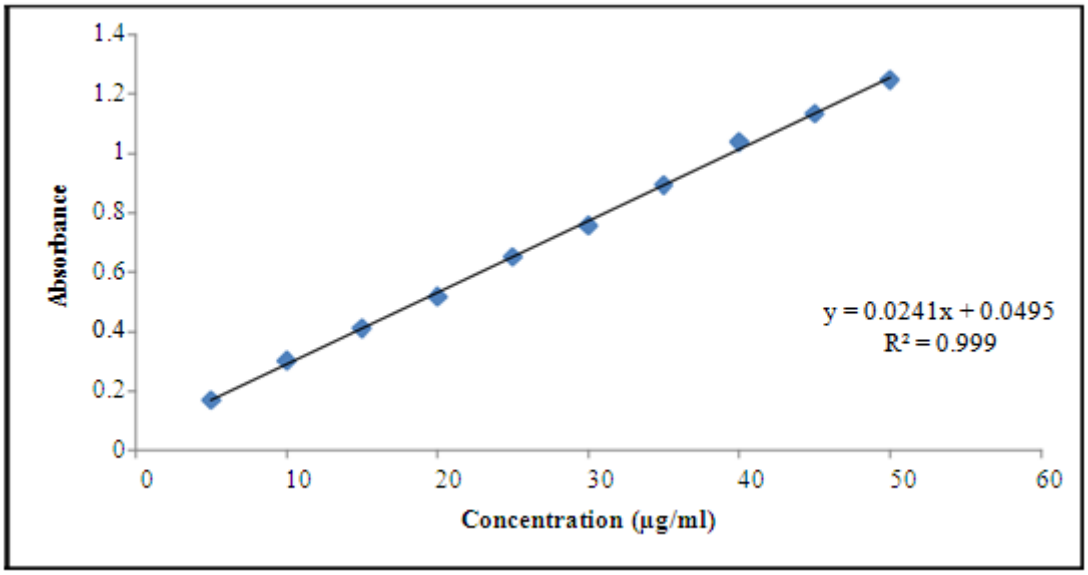
Table 3 Calibration Data for Tolbutamide in 0.1 N HCl

S. No.	Concentration (µg/ml)	Abs at 230 nm* (n=3)
1.	5	0.170+0.002
2.	10	0.302+0.005
3.	15	0.411+0.004
4.	20	0.518+0.004
5.	25	0.652+0.006
6.	30	0.758+0.005
7.	35	0.893+0.005
8.	40	1.038+0.005
9.	45	1.134+0.006
10.	50	1.247+0.004

* Results are expressed as Mean ± SD



(a)



(b)

Figure 3 (a): Overlay UV spectra of Tolbutamide in 0.1 N HCl **(b**) Calibration curve of Tolbutamide in 0.1 N HCl

Drug Excipient Compatibility Study

The FTIR scan of the drug, polymers and physical mixture of drug and polymers is recorded in figure 4.

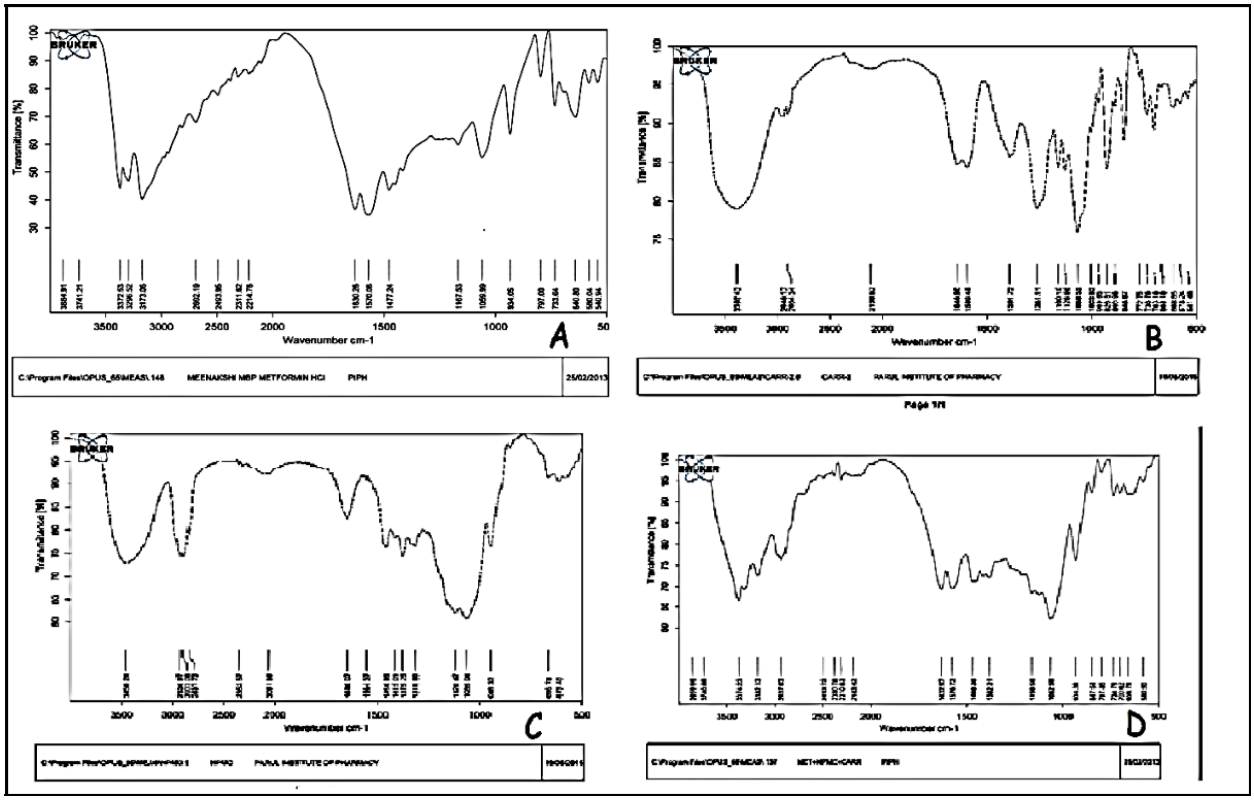


Figure 4 FTIR scan obtained for Tobutamide **(A)**, kappa carrageenan **(B)**, HPMC K15M **(C)** physical mixture of drug and polymers **(D)**

FTIR scan of tobutamide exhibited characteristic peaks at 3372.53 cm^{-1}, 3296.52 cm^{-1} and 3173.06 cm^{-1} for N-H asymmetric stretching, N-H symmetric stretching and symmetric N-H stretching, respectively. There was insignificant shift in the peaks observed in the FTIR scan of drug and polymer blend. It showed characteristic peaks at 3374.23 cm^{-1} and peaks at 3182.13 cm^{-1} for N-H asymmetric stretching and symmetric N-H stretching, respectively. Peak at 2692.19 cm^{-1} indicates CH3 symmetric stretching. Peaks at 1630.26 cm^{-1} and 1477.24 cm^{-1} correspond to CH3 asymmetric deformation and C = N stretching, respectively. All of these peaks were found in the infrared spectra produced from the drug-polymer mix, demonstrating that the drug and the other polymers are compatible.

Conclusion

Tolbutamide is administered orally in the form of simple tablets however, the maximum absorption of this drug takes place in stomach. It has limited absorption window in intestine and hence it should be confined to specific area of stomach for long duration to get the desired benefit at low dose. However, the physicochemical investigation was required to get an idea about whether this drug can be localized into the gastric environment for better efficacy. We have checked different physicochemical investigations of this drug. The solubility of tolbutamide supports its utility in the stomach as a gastro retentive system. At the same time, compatibility with the ingredient is essential when formulated in the form of tablets and beads. It was compatible with the ingredient used to prepare beads and tablets. Its suitable permeability may ensure good absorption from the gastric environment. In conclusion, Tolbutamide, if used as a gastro retentive drug delivery system, may work efficiently and will be able to improve the therapeutic effect allowing blood glucose levels to be maintained more effectively. However, further investigation is needed to justify its utility as a gastro retentive system in the efficient treatment of diabetes.

References

1. Lachman L.,Lieberman HA.,Kanig JL ,The theory and practice of industrial pharmacy,3RD edition, Varghese publishing house, Hind Rajasthan building, Dadar, Bombay-400014, pp 293.
2. Chien Yie W, Novel Drug Delivery Systems, vol 50, 2ND edition, Marcel Dekker, Inc, New York, Basel, Hongkong, pp 157.
3. Shivkumar HG, Gowda DV, Pramod KTM, 2003, Floating controlled drug delivery system for prolonged gastric residence : A Review, Ind. J. Pharm. Edu., 38(4): 172- 178.
4. Arora S, Ali J, Ahuja A, Khar RK, 2005, Floating drug delivery system: A Review, AAPS Pharm Sci. Tech.., 6(3): 372 – 379.
5. Choudhury Pk, Kar M, 2005, Preparation of Alginate gel beads containing Metformin hydrochloride using emulsion-gelation method, Tropical J. of Pharm. Res., 4(2): 489 – 493.
6. Wise D.L., Handbook of Pharmaceutical Controlled release Technology, Marcel Dekker, Inc. New york, pp 414-417.
7. Rowe RC, Sheskey PJ, Weller PJ, Handbook of Pharmaceutical Excipients, 4TH edition, Pharmaceutical press, APhA, pp 543-544.
8. BhardwajTR, Kanwar M, Lal R, 2000, Natural gums and modified natural gums as sustained release carriers, Drug development and

industrial pharmacy, 26(10): 1025-1038.

9. Rawlins EA. Bentley's text book of pharmaceutics. London, England: Cassell and Collier Macmillan. 1977.
10. Pani, N.R., Nath, L.K., Acharya, S. and Bhuniya, B., 2011. Application of DSC, IST, and FTIR study in the compatibility testing of nateglinide with different pharmaceutical excipients. *Journal of Thermal Analysis and Calorimetry*, *108*(1), pp.219-226.