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TO DEVELOP AND EVALUATE SUSTAINED RELEASE MATRIX TABLET OF REPAGLANIDE USING PROCESSED ALOE VERA MUCILAGE AS RELEASE MODIFIER

Pharmacy

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ABSTRACT

The main aim of present research was to formulate and evaluate the sustained release matrix tablets of Repaglinide (RPGN) with Aloe vera as release modifier. A sustained release tablet should release the desired quantity of drug with predetermined kinetics to maintain effective plasma concentration which can be done by formulating a tablet that releases the drug in a predetermined and reproducible manner. These matrix tablets were compressed using direct compression technique. Different tablet formulations were prepared using different drug: polymer ratio viz, 1:1, 1:2, 1:3, 1:4, and 1:5. Dry powdered mucilage extracted from Aloe vera leaves was evaluated for angle of repose, LBD, TBD, Carr's index, and Hausner's ratio. The prepared tablets were evaluated according to pharmacopoeial standards. It was observed from the kinetic studies that all the formulations followed first order kinetics and particularly the drug release from its dosage form. The present work clearly indicates the possible use of processed aloe vera gel (PAG) for modulating the drug release by using in varying ratios. We can conclude that the prepared matrix tablets using PAG as mucilage can be used as a release retardant in the formulation of sustained release matrix tablets.

KEYWORDS

Matrix tablets, natural polymers, repaglinide, synthetic polymers, PAG

GENERAL INTRODUCTION

The conventional dosage forms such as tablets and capsules are the major oral preparations and have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance in last two decades. Repaglinide i.e. (+) 2-ethoxy-4(2((3-methyl-1-(2- (1-piperidinyl) phenyl)- butyl) amino)-2-oxoethyl) benzoic acid is an oral anti-hyperglycemic agent used for the treatment of non insulin dependent diabetes mellitus (NIDDM). It belongs to the meglitinide class of short acting insulin secretagogues, which act by binding to the β cells of the pancreas to stimulate the insulin release. Considerable research had been done on the drug RPGN for sustained release and from the literature, it was found that they were developed sustained release matrix tablets of Repaglinide (RPGN) with Aloe vera as release modifier. The most commonly using method of modulating the drug release is matrix system and an effort was therefore made to develop simple and effective sustained release Repaglinide tablets using a polymer matrix system. In the present study, an attempt has been made to develop sustained release matrix tablets of Repaglinide using processed aloe vera mucilage as release modifier. The possible use of PAG for modulating the drug release by using in varying ratios. We can finally conclude that the prepared matrix tablets using PAG as mucilage can be used as a release retardant in the formulation of sustained release matrix tablets.

MATERIAL AND METHODS

Materials:

1. RPGN, HPMC K4M and HPMC 100M GG , CG and PVP , Magnesium stearate (MS) Talc Lactose was obtained.

100 tablets of Repaglinide were obtained

- Drug excipient compatibility studies were conducted.
- The pure drug and its physical mixtures were subjected to IR spectral studies using FTIR spectrophotometer in the wave number region from 4000 cm-1 to 400 cm-1. The spectra obtained for pure drug and the physical mixtures were compared.
- Evaluation studies.
- Drug Content (Assay).
- Kinetic analysis of dissolution data.
- Stability studies.
- Compatibility studies

2. Extraction of aloevera mucilage

- Aloevera fresh plant leaves were collected and washed with water to remove dirt and debris.
- Incisions to be made on leaves and soaked in water for 5-6 hrs, and boiled for 30 mins and allowed to stand for 1hr for release of mucilage in water.
- The material was then squeezed from cloth to remove marc from the solution.
- Three volumes of acetone were added to the filtrate to precipitate the mucilage.
- The mucilage was separated and dried in an oven at a temperature of <50 degree celcius.
- Dried powder was passed through No. 80 sieve and to be storedin dessiccator for further use.
- Flow properties were evaluated.
- Bulk density was evaluated.
- Compressibility index

3. Preparation of matrix tablets: Different tablet formulations to be prepared using different drug: polymer ratio viz,1:1,1:2,1:3,1:4,1:5. Powder blend was evaluated before compression.
4. Evaluation of powder blend.
5. Evaluation of tablets Thickness.
6. Weight variation test.
7. Hardness and friability.
8. Drug content.
9. Swelling characteristics.
10. In vitro release studies.
11. Kinetic release profile.
12. Accelerated stability studies

Table 1: Composition of matrix tablets of Repaglinide containing varying ratios of PAG Ingredients Formulation code

Ingredients	Formulation Code				
	PAG1 (mg)	PAG2 (mg)	PAG3 (mg)	PAG4 (mg)	PAG5 (mg)
Repaglinide	15	15	15	15	15
PAG	15	30	45	60	75
Microcrystalline cellulose	168	153	138	124	108
Magnesium stearate	4	**4**	**4**	**4**	**4**

PAG – Processed Aloe vera gel

During the development of a formulation, the flow of the blend can affect the selection of an excipient and gives information whether direct compression is required, or other granulating techniques have to be used. Therefore, dry powdered mucilage extracted from *A. vera* leaves was evaluated for angle of repose, LBD, TBD, Carr's index, and Hausner's ratio [Table2]. The results of angle of repose and Carr's index (%) were 21.87±0.32, 12.44±0.11respectively. The results of LBD and TBD were 0.47±0.02, 0.89±0.06 respectively. The Hausner's ratio was found to be 1.189±0.04. The flow properties of the powder

blend was also determined. The angle of repose and Carr's index (%) ranged from 20.56 ± 0.022 to 23.83 ± 0.021 and 12.40 ± 0.88 to 15.886 ± 1.56, respectively. The results of angle of repose (<30) indicate good flow properties of the granules. This was further supported by lower Carr's index values [Table 4]. Generally, compressibility index values up to 15% result in excellent flow properties. The results of LBD and TBD ranged from 0.40±0.03 to 0.46±0.03 and 0.55±0.01 to 0.59 ± 0.03, respectively.

Table 2: Showing Flow properties of Aloe vera Mucilage

Parameter	Value
Angle of response (°)	21.87±0.32
Loose bulk density (g/cm3)	0.47±0.02
Tapped bulk density (g/cm3)	0.89±0.06
Carr's index	12.44±0.11
Hausner's factor	1.189±0.04

- **Effect of Aloe vera gel on biological membrane permeation Intestinal drug absorption enhancement**

The effect of *A. vera*gel and whole leaf extract on the oral bioavailability of vitamins C and E wasinvestigated in humans in a randomised, double-blind, cross-over clinical trial. Both the gel and wholeleaf extract decreased the rate of vitamin C absorption, but the overall bioavailability (area-undercurve)of vitamin C was 3 times higher when administered with the aloe gel as compared to the controland the gel kept the level of this vitamin significantly higher ($p \leq 0.05$) than the baseline even after 24hours. The bioavailability of vitamin C administered in conjunction with the whole leaf extract wasonly 80 % compared to the control and the level returned to baseline after 24 hours. For vitamin E, thebioavailability was 3.7 times higher when administered with aloe gel and 2 times higher with the aloewhole leaf extract. The mechanism of action of the aloe products to improve the bioavailability of thevitamins was explained to be a possible protection effect against the degradation of the vitamins in theintestinal tract as well as binding of the polysaccharides to the vitamins and thereby slowing down theabsorption rate.[4]

It is well known that polysaccharides of natural origin such as chitosan are capable of enhancing theintestinal absorption of co-administered drugs by means of a transient opening of the tight junctionsbetween adjacent epithelial cells to allow for paracellular transport across the intestinal epithelium.[44,45] In a recent *in vitro* study it was shown that both *A. vera* gel and whole leaf extract coulddecrease the transepithelial electrical resistance of intestinal epithelial cell monolayers (Caco-2),thereby indicating opening of the tight junctions between adjacent epithelial cells. The *A. vera*gel andwhole leaf extract were also able to significantly increase the transport of the macromolecular peptidedrug, insulin, across the Caco-2 cell monolayers. The cumulative transport of insulin in the absence(control) and presence of different concentrations of A. vera gel at pH 7.4 is depicted in Figure 1.

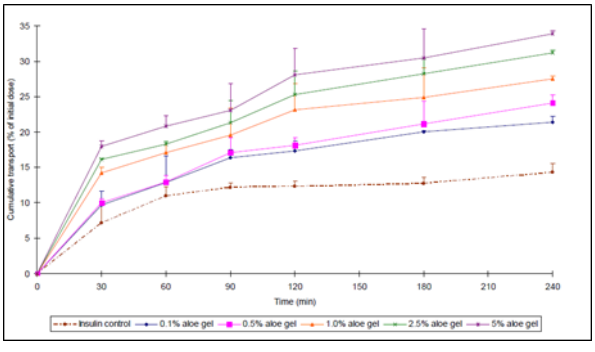

Figure 1: The effect of *A. vera* gel on the transport of insulin across Caco-2 cell monolayer's at pH 7.4.

Table 3: Precompressive parameters of blend (n = 3)

Loose bulk density (g/ml)	Tapped bulk density (g/ml)	Hausnersfactor	Angle Ofrepose (°)	Carr's index (%)
0.44±0.04	0.58±0.02	1.184±0.022	23.35±0.01	13.34±1.80
0.45±0.06	0.59±0.03	1.196±0.14	20.48±0.02	12.41±1.40
0.46±0.03	0.58±0.05	1.201±0.21	24.44±0.02	15.99±1.56
0.41±0.04	0.55±0.01	1.227±0.45	22.36±0.06	12.32±0.88
0.40±0.03	0.56±0.04	1.246±0.32	21.91±0.03	14.54±1.48

Table 4: Post compressive parameters of matrix tablets

Formulation code	Thickness (mm) n = 3	Weight variation (mg)n = 20	Hardness (kg/cm2) n = 10	Friability (%) n = 10	Drug content (%)n = 20
PAG1	3.3±0.1	200±2.01	6.6±0.1	0.077±0.31	99.12±0.1
PAG2	3.5±0.2	197±2.31	5.7±0.2	0.083±0.30	98.67±0.4
PAG3	3.6±0.3	203±3.11	6.2±0.1	0.085±0.35	98.96±0.3
PAG4	3.2±0.3	202±2.15	6.1±0.2	0.087±0.13	99.22±0.2
PAG5	3.3±0.1	201±2.24	6.4±0.2	0.081±0.32	98.10±0.3

The swelling index of the prepared tablets was determined [Table 6]. It was observed that swelling index increased with time but later on it decreased. The percentage of swelling was greater in formulation PAG5 which possessed greater concentration of *A. vera*mucilage.

The drug release kinetic data were for all the formulation is also shown in Table 6. The kinetics data obtained from the studies reveals that formulations follow zero-order release kinetics and the rate of drug release is independent of concentration.

Drug release of the formulation PAG1, PAG2, PAG3, PAG4 and PAG5 had the regression data were of 0.9858, 0.9756, 0.9865, 0.9884 and 0.9944 respectively, exhibiting zero order kinetics. According to Koresmeyer equation, the formulation PAG1, PAG2, PAG3, PAG4 and PAG5 exhibited the regression values of 0.9892, 0.9846, 0.9817, 0.9784 and 0.9688 respectively. The plot for (log cumulative percentage drug release vs. time) Koresmeyer–Peppas equation correspondingly indicated good linearity for the commercially available SR tablet and formulation PAG5 with regression values of 0.9688 and 0.9944, respectively. The release component n was found to be 0.5145 and 0.6580 respectively. Optimized formulation was subjected to accelerated stability studies. Various parameters like hardness and drug content were retained by the optimized formulation on storing it at varying temperature conditions.

Table 5: Correlation coefficients according to different kinetic equations

Formulation	Zeroorder	First order	Higuchi model	Koresmeyer model	
		r2		N	r2
PAG1	0.9858	−0.8953	0.9834	0.7249	0.9892
PAG2	0.9756	−0.9025	0.9712	0.7015	0.9846
PAG3	0.9865	−0.9154	0.9674	0.6852	0.9817
PAG4	0.9884	−0.9461	0.9617	0.6741	0.9784
PAG5	0.9944	−0.8257	0.9488	0.6580	0.9688

Table 7: Physical and chemical parameters of formulated tablets stored at 45°C (n = 10)

Formulation	Time	Appearance	Hardness	Drug content
PAG5	Initial	Pale white	6.0±0.12	99.84±0.43
	30 days	Pale white	5.4±0.16	99.84±0.32
	60 days	Pale white	5.4±0.16	99.84±0.02
	90 days	Pale white	5.4±0.16	98.52±0.21

SUMMARY AND CONCLUSION:

Diabetes Mellitus is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar. Hyperglycemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels.

Glinides, a new class of short acting insulin secretagogues act directly on the pancreatic beta cell to stimulate rapid insulin secretion Repaglinide is the first oral agent of the meglitinide class to become available for the treatment of type 2 diabetes. One of the many advantages of Repaglinide is that it is one of the few oral agents that can be used in chronic renal failure. The gretest disadvantage of Repaglinide is that it has a very short elimination half-life (1 h) hence it is challenge in development of oral controlled release drug is not just to sustain the drug release but also to prolong the presence of the dosage form within the gastrointestinal tract until all the drug is completely released at the desired period of time.

Aloevera is known for many health benefits including wound healing, antifungal activity, hypoglycemic or antidiabetic effects anti-

inflammatory, anticancer, immunomodulatory and gastroprotective properties. Recently is has been discovered that both the A. vera gel and whole leaf extract have the ability to improve the bioavailability of co-administered vitamins in human subjects. Hence the aim of this study to develop and evaluate sustained release matrix tablets of repaglinide using processed aloe Vera mucilage as release modifier

Different tablet formulations were prepared using different drug: polymer ratio viz, 1:1, 1:2, 1:3, 1:4, 1:5. dry powdered mucilage extracted from A. vera leaves was evaluated for angle of repose, LBD, TBD, Carr's index, and Hausner's ratio. The flow properties of the powder blend was also determined. The results of angle of repose (<30) indicate good flow properties of the granules. Compressibility index values in our result showed excellent flow properties. Tablets with different formulation codes were subjected to various evaluation tests, such as thickness, hardness, friability, and uniformity of drug content. All the formulations showed uniform thickness (CV <0.5%), uniform weight with little significance difference ($P > 0.1$) were observed with varying formulation code. The percentage friability for all the tablet formulations was below 1%. Drug content was found to be uniform among different batches. It was observed that swelling index increased with time but later on it decreased. The kinetics data obtained from the studies reveals that formulations follow zero-order release kinetics and the rate of drug release is independent of concentration.

Our results clearly indicate the possible use of PAG for modulating the drug release by using in varying ratios. From the above studies, we can finally conclude that the prepared matrix tablets using PAG as mucilage can be used as a release retardant in the formulation of sustained release matrix tablets.

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