Original Article

Studies on the Applicability of Natural Gums, Neem Gum and Tamarind Gum as Release Controlling Polymers

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Abstract

Development and evaluation of matrix tablets of vildagliptin was proposed in the present investigation with a view of studying the applicability of two natural gums, neem gum and tamarind gum as release controlling polymers. HPMC K100 was used a reference polymer owing to its established release controlling property. Preliminary drug-excipient compatibility studies were done and confirmed the lack of incompatibility among the formulation ingredients. Precompression properties and tablet characteristics were evaluated and the results were analysed meeting the desired levels. HPMC based tablets shown prominent drug release, however the selected natural gums were proved to show controlled drug release up to 24 hours and is observed as polymer concentration dependant.

1. INTRODUCTION

Gums, mucilages and pectins are widely used natural excipients for conventional and novel dosage forms. These naturally derived polymers have become a subject of increasing interest to discover, extract and purify such compounds from the natural origin. Keeping in view of this demand researchers are exploring different plant exudates for their excipient applicability in the design of different dosage forms[1].

Large number of gums, polysaccharides and hydrogels were reported in the development of modified release formulations. Natural gums are preferred over semisynthetic and synthetic polymers due to the following advantages[2,3]. Natural gums were found to be highly inert physically and chemically since, they found to be withstanding on barks in extreme weather conditions. Few natural gums show good aqueous solubility because of polysaccharide structure. Swelling and gelling nature of natural gums supports the modification of drug release behaviour hence, effectively utilized for retarding the drug release from tablet dosage forms. The gums are originated from cellular sources of plants, represents as a renewable source without adverse effects to human and environmental health. Most of the gums are biocompatible and non-toxic, chemically gums are carbohydrates, polysaccharides in nature which hydrolyse as monosaccharides which are highly safer and easily metabolised. Non-toxic nature, wide availability also increased the exploitation of the usage of gums for various applications.

The present work was aimed to extend the drug release of selected model drug vildagliptin from matrix dosage forms by using the two natural release controlling polymers of *Azadirachta indica* (neem gum) and *Tamarindus indica* (tamarind gum).

2. MATERIALS AND METHODS

Neem gum is a natural exudate extracted from the naturally held injury on the bark of neem tree *Azadirachta indica*[4-8]. Tamarind gum is obtained from *Tamarindus indica* belonging to Leguminosae/Fabaceae family[9-12]. Semisynthetic polymer hydroxyl propyl methyl cellulose K100M (HPMC K100M) was used a reference polymer to study the performance of the selected two gums. PVP K30, a synthetic polymer was selected as binder[13-14]. Lactose monohydrate was used as diluent and magnesium stearate as lubricant.

Vildagliptin is a new oral hypoglycaemic agent of the new dipettidyl peptidase–DPP-4 inhibitor class of drugs[15-19]. Vildagliptin inhibits the inactivation of GLP-1 and GIP by DPP-4. It allows the GLP-1 and GIP to potentiate the secretion of insulin in the beta cells and supress glucagon release by the alpha cells of the islets of Langerhans in the pancreas.

2.1. Drug-excipient compatibility study

The compatibility studies were performed for drug-excipient physical mixtures and the compositions of physical mixtures studied for compatibility are shown in **Table 1.** Drug and excipient mixtures were mixed properly in proportions of 1:3

and packed in amber glass vial and closed with elastomeric closure, then compatibility study was done by storing at different temperature conditions 40±2°C, 75±5% relative humidity and 50±2°C for four weeks and evaluated after intervals of 2 weeks[20]. No relative humidity was considered for 50±2°C temperature conditions. For comparison, pure drugs and excipients were also stored under similar conditions and evaluated. After two week intervals, the samples were visually inspected for any physical changes by comparing with initial samples kept as control at ambient conditions and physical mixtures were tested for respective drug content and compared with respective initial drug content values.

Table 1: Physical mixtures used for drug-excipient compatibility study

Sample code	Sample details	Ratio
V	Vildagliptin	Neat Sample
N	Neem gum	Neat Sample
T	Tamarind gum	Neat Sample
L	Lactose monohydrate	Neat Sample
M	Magnesium Stearate	Neat Sample
P	PVP	Neat Sample
VN	Vildagliptin + Neem gum	1:3
VT	Vildagliptin + Tamarind gum	1:3
VL	Vildagliptin + Lactose monohydrate	1:3
VP	Vildagliptin + PVP	1:3
VM	Vildagliptin + Magnesium stearate	1:3

2.2. Preparation of precompression blend

The dose of vildagliptin was used as 100 mg/tablet[21]. Extended release matrix tablets were prepared by wet granulation method. All the ingredients sufficient for a batch of tablets were weighed and passed through sieve #100 (aperture size 150 µm). The composition of the prepared tablets is shown in **Tables 2 and 3**. The ingredients were geometrically mixed for forming uniform blend except magnesium stearate. 30% v/v isopropyl alcohol in water was used as granulating agent and sufficient quantity was added to the powder blend for formation of dough mass. Granules were prepared by passing wet mass initially through sieve #12 (aperture size 1.4 mm) and dried at 50°C in hot air oven until moisture content reaches in the range of 2 to 3 % w/w. Dried granules were passed through sieve #22 (aperture size 710 µm). Then granules were lubricated with magnesium stearate in a polybag. Flow properties of the powder blends were conducted.

2.3. Evaluation of precompression blend for flow properties

The powder blends of all formulations were evaluated for flow properties (angle of repose, Carr's index (CI) and Hausner's ratio (HR). All these trials are made in triplicate and average values are reported.

Table 2: Composition of vildagliptin tablets using HPMC

Ingredient (mg)	VH1	VH2	VH3	VH4	VH5
Vildagliptin	100	100	100	100	100
HPMC	10	45	80	115	150
PVP	10	10	10	10	10
Lactose monohydrate	150	115	80	45	10
Magnesium stearate	5	5	5	5	5
Tablet weight (mg)	**275**	**275**	**275**	**275**	**275**

Table 3: Composition of vildagliptin tablets using natural gums

Ingredient (mg)	VN1	VN2	VN3	VN4	VN5	VT1	VT2	VT3	VT4	VT5
Vildagliptin	100	100	100	100	100	100	100	100	100	100
Neem gum	10	45	80	115	150	-	-	-	-	-
Tamarind gum	-	-	-	-	-	10	45	80	115	150
PVP	10	10	10	10	10	10	10	10	10	10
Lactose monohydrate	150	115	80	45	10	150	115	80	45	10
Magnesium stearate	5	5	5	5	5	5	5	5	5	5
Tablet weight (mg)	**275**	**275**	**275**	**275**	**275**	**275**	**275**	**275**	**275**	**275**

2.4. Compression of tablets

The final blend was compressed into tablets on a 16-station rotary punching machine (M/s. Cadmach Machinery Co. Pvt. Ltd., India) using 7.2 mm, round flat faced punches with a compression force sufficient to obtain hardness 8 to 12 kp.

2.5. Evaluation of matrix tablets

Compressed tablets were evaluated for tablet properties of thickness, hardness, friability, uniformity of weight and percent drug content[22].

2.6. *In vitro* dissolution studies

Drug release from the matrix tablets of vildagliptin[23] was studied using USP type-I (basket) dissolution apparatus, in 900 mL of pH 6.8 phosphate buffer for 24 hours at 37±0.5ºC at 75 rpm. 5 mL of dissolution medium was withdrawn using a

syringe fitted with 0.45 µm pre filter at regular time intervals and the same volume of (37±0.5ºC) fresh dissolution medium maintained at 37±0.5ºC was replaced. The samples were diluted wherever necessary and analyzed spectrophotometrically. The cumulative percent of drug released at different time intervals was calculated. All the dissolution studies were presented as average values with % relative standard deviation (%RSD).

2.7. Drug release kinetics and mechanism

The rate and mechanism of drug release play an important role in assessing the quality of the dosage form and also for achieving the desired time of drug action in the body for controlled release dosage forms. The drug release kinetics was evaluated by fitting the data to zero and first order[24,25]. Mechanism of drug release was evaluated by fitting the data to Higuchi diffusion model, erosion model and further characterized by using Korsmeyer-Peppas equation[26-29].

3. RESULTS AND DISCUSSION

3.1. Drug-excipient compatibility study

No significant physical change was observed including color in all samples after 4th week. The drug content also remained unchanged compared to initial sample after 4th week as detailed in **Table 4** indicating no degradation of vildagliptin with the excipient mixtures studied. Compatibility studies conducted through accelerated stability condition on vildagliptin with both neem gum and tamarind gum and other excipients showed no significant differences in the physical state and drug content between the initial, 2nd week and 4th week samples indicating compatibility between the drug, gums and other selected excipients. Hence, formulation studies are conducted with the proposed drug, gums, and excipients.

Table 4: Drug content estimation in the stability samples (mean±s.d., n=3)

Sample Code	Respective drug content in the physical mixtures				
	Initial	40±2°C/75±5% RH		50±2°C	
		2nd week	4th week	2nd week	4th week
V	99.23±1.22	99.58±0.89	99.38±1.12	99.38±0.66	99.68±0.93
VN	99.95±0.15	99.55±0.51	99.65±0.99	99.55±0.86	99.91±0.25
VT	99.67±1.06	99.71±0.11	99.09±0.99	99.70±1.04	99.53±0.58
VL	99.65±1.00	99.14±0.66	99.94±0.86	100.12±0.46	99.63±1.02
VP	99.26±0.59	99.74±0.14	99.14±0.42	99.22±0.67	99.61±0.31
VM	99.36±0.69	99.68±0.16	98.83±0.46	99.35±0.67	99.33±0.68

3.2. Evaluation of precompression blend for flow properties

Particle size distribution, particle shape and tendency of the particles to adhere together play an important role in the filling of hopper and compression of tablets. The micromeritic properties such as angle of repose, Carr's index and Hausner's ratio are the parameters used for evaluating the flow properties, ease of consolidation of powder and inter particulate friction respectively.

Results of micromeritic parameters of precompression blends of all the formulations are given in **Tables 5**. Carr's Index and Hausner's ratio were calculated from average values of tapped and bulk densities. The angle of repose values were in the range of 30.12-34.41° while CI was between 11.63 and 14.81. Hausner ratio of all the formulations was in the range of 1.13 to 1.17 and all these values indicated that the precompression blends were showing good flow to excellent flow properties with low inter particle friction.

Table 5: Flow properties of vildagliptin precompression blends (mean±s.d., n=3)

Formulation code	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index (%)	Hausner's ratio	Angle of repose (º)
VH1	0.48±0.023	0.56±0.021	14.29	1.17	30.38±0.83
VH2	0.46±0.021	0.52±0.023	11.54	1.13	31.42±0.67
VH3	0.42±0.012	0.48±0.023	12.50	1.14	34.02±0.95
VH4	0.46±0.019	0.54±0.019	14.81	1.17	33.26±0.68
VH5	0.52±0.021	0.6±0.016	13.33	1.15	30.68±0.79
VN1	0.36±0.031	0.43±0.016	14.29	1.17	31.11±0.58
VN2	0.35±0.016	0.42±0.014	12.50	1.14	33.20±0.67
VN3	0.37±0.019	0.44±0.021	11.90	1.14	34.41±0.65
VN4	0.35±0.021	0.40±0.036	12.50	1.14	33.82±0.88
VN5	0.36±0.025	0.42±0.024	14.29	1.17	32.32±0.59
VT1	0.37±0.024	0.43±0.016	13.95	1.16	31.42±0.69
VT2	0.38±0.015	0.45±0.017	11.63	1.13	30.12±0.88
VT3	0.32±0.018	0.38±0.021	14.29	1.17	31.19±0.58
VT4	0.31±0.021	0.37±0.026	13.95	1.16	32.16±0.37
VT5	0.35±0.028	0.42±0.032	14.63	1.17	33.20±0.87

3.3. Evaluation of matrix tablets

The tablet properties of vildagliptin formulations are given in **Table 6**. The tablets were found to be off white to pale yellow in color and round. The thickness of vildagliptin tablets was in the range of 5.15-5.26 mm. The hardness of all the matrix tablets was in the range of 9-11 kp. The matrix tablets passed the friability test as the % loss during the test was less than 1% confirming to the compendial limits. The tablets confirmed to the uniformity of weight test as the % deviation

of weight was less than ±5%, complying with pharmacopeial specifications. The drug content of each individual preparation was found to be within the specified limits of 90 to 110% of the stated amount.

Table 6: Evaluation of vildagliptin matrix tablets

Formulation	Thickness[a] (mm)	Hardness[a] (kp)	Friability[b] (%)	Average weight of tablets[c] (mg)	Drug content[d] (%)
VH1	5.00 ±0.02	10 ±0.57	0.38	276.21 ±3.125	102.2±0.31
VH2	5.10 ±0.05	10 ±0.84	0.32	275.02 ±2.136	101.1±0.95
VH3	5.15 ±0.06	10 ±0.57	0.29	274.96 ±2.136	100.6±0.91
VH4	5.20 ±0.06	10 ±0.65	0.15	276.52 ±1.589	100.6±0.25
VH5	5.25 ±0.07	11 ±0.78	0.14	275.42 ±3.265	100.4±0.65
VN1	5.00 ±0.05	9 ±0.87	0.48	276.18 ±4.568	99.8±1.03
VN2	5.15 ±0.04	10 ±0.25	0.35	274.64 ±2.365	97.2±0.20
VN3	5.20 ±0.03	10 ±0.36	0.24	275.21 ±2.345	98.9±0.35
VN4	5.24 ±0.06	10 ±0.45	0.22	273.81 ±1.895	98.2±0.32
VN5	5.29 ±0.05	11 ±0.58	0.19	275.08 ±3.214	100.2±0.60
VT1	5.00 ±0.07	9 ±0.68	0.42	274.68 ±2.365	101.3±0.86
VT2	5.10 ±0.06	10 ±0.78	0.38	275.35 ±3.859	103.1±0.44
VT3	5.15 ±0.04	10 ±0.84	0.31	274.92 ±2.325	100.2±0.70
VT4	5.23 ±0.03	10 ±0.78	0.24	275.61 ±1.985	100.5±0.49
VT5	5.29 ±0.03	11 ±0.81	0.16	275.24 ±2.314	101.5±0.38

a: mean±s.d., n=6; b: n=12 tablets (~ 6.6g); c: mean±% deviation, n=20; d: mean±s.d., n=3

3.4. *In vitro* dissolution studies

The dissolution profiles of vildagliptin are shown in **Figures 1-3**. Among vildagliptin formulations, the composition VH5 (with HPMC) extended the drug release up to 27 hours whereas, the formulations VT5 (with tamarind gum) and VN5 (with neem gum) complete drug release was observed within 24 hours.

Formulations with lower polymer concentrations (percentage of polymer to drug 10%, 45%) rapidly hydrated, resulting in weak matrix systems and could not extend the release beyond 4 to 6 hours. With further increase in polymer concentrations to 80, 115 and 150%, thicker gel formed inhibiting the dissolution media into matrix structure which could be due to closely packed swollen particles in thick gel and drug release was retarded significantly. The amount of polymer in the formulation was found to affect the drug release rate which could be due to the high viscosity of the gel layer around the drug in the tablet increases with increase in polymer concentration thus limiting the release of the drug.

Physical observations of the tablets in the dissolution apparatus were found to have a gel structure that erode fast with lower polymer content matrix tablets compared to the gel structure of the matrix tablets remained uneroded and intact with higher polymer content matrix tablets. Matrix tablets with higher content of HPMC and gums showed good hydration, less erosion but viscous gel mass remained even after complete release of the drug with matrix tablets of HPMC and little gel mass remained for matrix tablets of neem and tamarind gums. Drug release from the matrix tablets was depended on type of polymer and concentration of polymer. HPMC found to retard the drug release up to 27 hours whereas neem and tamarind gum retarded the drug release up to 24 hours.

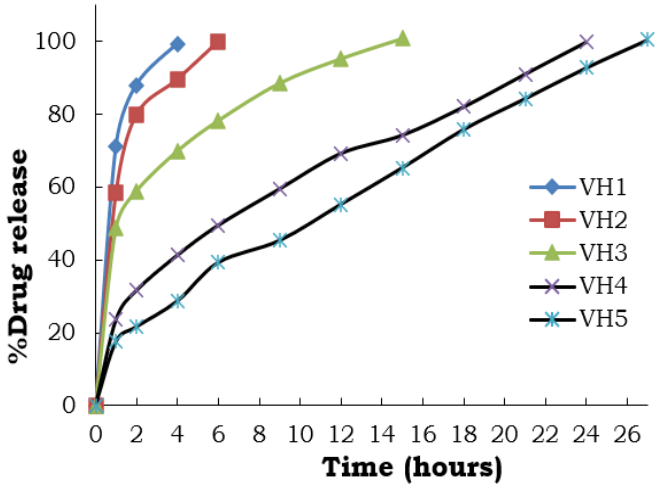

Figure 1: *In vitro* drug release profiles of vildagliptin matrix tablets (VH1-VH5)

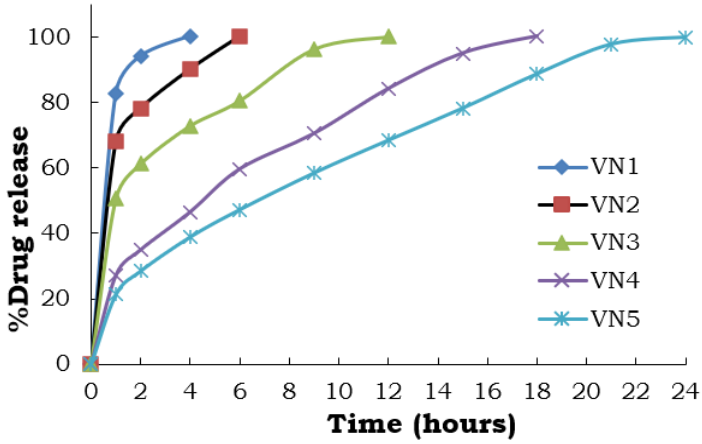

Figure 2: *In vitro* drug release profiles of vildagliptin matrix tablets (VN1-VN5)

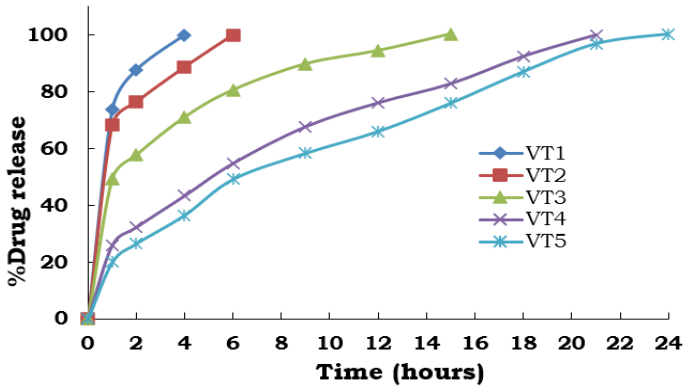

Figure 3: *In vitro* drug release profiles of vildagliptin matrix tablets (VT1-VT5)

3.5. Evaluation of drug release kinetics and mechanisms

The order of release of all the formulations of vildagliptin were evaluated and compiled in **Table 7** respectively. The correlation coefficient values indicated that all the formulations of all the three polymers, HPMC, neem gum and tamarind gum followed first order release with lower polymer content (10% to 80%) and followed zero order with high polymer content (115% and 150%) in the tablet compositions.

The release mechanism was evaluated by using Higuchi, erosion and Korsmeyer-Peppas equation. The correlation coefficient (r) and Peppas exponent (n) values are shown in **Table 7**. Correlation coefficient of Higuchi's plot of all formulations showed high linearity, indicating the drug release from matrix tablets involved diffusion, which means transport of drug from the matrix tablet into the dissolution media depending on the concentration. Korsmeyer-Peppas plot and 'n' values, indicated that the drug transport mechanism follows either case II transport or super case II transport and drug release mechanism to be zero order release or relaxation/erosion mechanism. Vildagliptin matrix tablets prepared using semisynthetic polymer HPMC and natural polymers neem and tamarind gums exhibited similar drug release parameters with both release order and release mechanisms, these polymers undergo diffusion in the aqueous medium due to solvent penetration effect, swelling, and polymer chain disentanglement and relaxation and these observations are in line with the reported literature[30-31].

Table 7: Release kinetics and mechanisms of vildagliptin matrix tablets

Formulation	Zero order		First order		Higuchi	Erosion	Korsmeyer-Peppas
	r	k_0 (%hr^{-1})	r	k_1 (hr^{-1})	r	r	n value
VH1	0.8399	21.9327	**0.9967**	0.5279	**0.9667**	0.7427	1.9459
VH2	0.8462	13.9641	**0.9045**	0.6012	**0.9671**	0.7036	1.5145
VH3	0.8503	5.0764	**0.8622**	0.2018	**0.9615**	0.6411	1.0435
VH4	**0.9631**	3.5079	0.8183	0.0772	**0.9981**	0.7419	0.8638
VH5	**0.9891**	3.3854	0.7439	0.0870	**0.9905**	0.8089	0.8890
VN1	0.7781	21.2954	**0.9787**	0.9982	**0.9341**	0.7171	1.9002
VN2	0.8144	13.3659	**0.9034**	0.5957	**0.9503**	0.6836	1.4709
VN3	0.8571	6.6122	**0.8963**	0.2783	**0.9670**	0.6470	1.0602
VN4	**0.9592**	4.9792	0.8267	0.1600	**0.9987**	0.7416	0.9783
VN5	**0.9733**	3.8124	0.8733	0.0939	**0.9980**	0.7698	0.9023
VT1	0.8337	21.8680	**0.9809**	0.6976	**0.9636**	0.7393	1.9364
VT2	0.8188	13.3031	**0.9259**	0.4419	**0.9514**	0.6851	1.8689
VT3	0.8452	5.0670	**0.8580**	0.2001	**0.9596**	0.6405	1.1969
VT4	**0.9584**	4.1282	0.8562	0.0937	**0.9990**	0.7396	0.9153
VT5	**0.9750**	3.8097	0.7988	0.1093	**0.9975**	0.7768	0.9138

4. CONCLUSION

The selected drug vildagliptin showed no drug-excipient interaction with the selected two natural gums neem and tamarind and synthetic polymer HPMC along with other excipients. Wet granulation technique was used for preparation of matrix tablets of vildagliptin using PVP as binding agent. The granules prepared by wet granulation showed good to excellent flow properties. All the prepared matrix tablets exhibited acceptable official and other tablet properties indicating their quality. The drug release from the matrix tablets depended on the polymer concentration and increase in polymer concentration retarded the drug release effectively. HPMC retarded the drug release more compared to the two natural polymers at the concentration of 150% of drug. However, the drug release was extended up to 24 hours with both gums and the drug release followed zero order release kinetics with diffusion mechanism. Hence it can be concluded that that natural gums, neem and tamarind gum have potential to control the release based on the used concentration.

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