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Research Article

EFFECT OF NATURAL POLYMERS AND EXCIPIENTS OF DRUG FREE TABLETS ON GASTRO RETENTIVE BEHAVIOUR

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ABSTRACT

The present task was taken up to formulate & evaluate dummy tablets using different natural polymers & effervescent agent to evaluate their effect on floating behaviour & to discover their feasibility for Gastro retentive tablets. Psyllium husk, Tara gum & Gellan gum were utilized as natural polymers in different concentrations. Dummy tablets were prepared with Wet Granulation Technique & evaluated mainly for Hardness, *In vitro* Buoyancy & Floating Time. All the natural gums were found to give good result by keeping the characteristics of different polymers in view. Gellan gum was found to give very good hardness of approx. 4.00 Kg/Cm^2. Psyllium husk was found to give excellent *In vitro* Buoyancy of up to 8 Sec. Tara gum was found to give comparatively good *In vitro* Buoyancy. All the natural polymers were found to give extraordinary Floating Time of about 24 hrs. Based on the above observations, it could be concluded that all the natural polymers have significant influence on the floating behaviour of the gastro retentive tablets.

Keywords: Gastro retentive, In vitro Buoyancy, Gellan Gum, Tara Gum, Psyllium Husk.

INTRODUCTION

The ultimate aim of oral controlled drug delivery system (CDDS) is to prolong the drug release to achieve better bioavailability. But this is somewhat difficult mainly due to short gastric residence time (GRT) & unpredictable gastric emptying time (GET).[1] Because of short GRT & unpredictable GET, there is occurrence of non uniform absorption profiles & incomplete drug release from the dosage form. These lead to incomplete absorption of drugs have narrow absorption window i.e. in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed.[2] To overcome these problems, different approaches of Gastro retentive drug delivery system (GRDDS) have been proposed such as floating system, swellable/expandable system, mucoadhesive system & high density/non effervescent system to retain the dosage form in the stomach for prolonged period time with predictable GET & longer GRT.[3]

GRDDS plays a vital role among novel drug delivery systems (NDDS). It helps the dosage forms (DFs) to be retained in the stomach for a prolonged period of time by making use of natural polymers such as Psyllium husk powder, Gellan gum & Tara gum; effervescent agent such as sodium bicarbonate, citric acid, calcium carbonate, calcium chloride & sodium citrate. These natural polymers are used as release retardant & effervescent agents are used to produce effervescence by reacting with 0.1 N HCl & thereby making the dosage form buoyant in the dissolution fluid i.e. 0.1 N HCl. Floating tablets were formulated by making use of both single natural polymer & combination of natural polymer with synthetic polymer i.e. HPMC K4M.

Gellan gum is an exocellular polysaccharide secreted by Pseudomonas elodea, with a tetrasaccharide-repeating unit of one α-L-rhamnose, one β-D-glucuronic acid, and two β-D-glucose residues.[4] It is Soluble in water, forming viscous solution; insoluble in ethanol.[5] Psyllium husk possesses good swelling &

gelling properties and therefore, when used as a matrix forming agent in the modified release formulation, it forms a swollen gel & control drug release.[6] Tara gum is obtained from the kernels (seeds) of the tara shrub Caesalpinia.[7]

MATERIALS AND METHOD

Gellan Gum was a gift sample from CP Kelco, A Huber Company, Mumbai. Tara Gum was a gift sample from TIC Gums, Maryland, USA. Psyllium Husk was obtained from Green Cross Remedy, Sidhpur, Mehsana. Spray dried lactose was a gift sample from Kawarlal & Co., Chennai. All other chemicals including HPMC K4M used were of analytical grade & obtained from Laboratory Sulab Reagent, Baroda.

METHODS

Formulation of Dummy Tablets by Wet Granulation Technique

Natural polymers, effervescent agents, HPMC K4M, Polyvinyl Pyrrolidone K 30 (PVP K 30) & diluents were weighed accurately & mixed in a mortar. Iso Propyl Alcohol was used as a Granulating Fluid (GF). Later on to improve the hardness of the tablets, acacia & tragacanth mucilage were used as GF. GF was added until a lump mass was produced. This wet mass was passed through 10 # sieve & then it was air dried (in case of acacia & tragacanth mucilage, dried in Hot Air Oven for 30 minutes) for 20 minutes. Dried powder was then passed through 22/44 # sieve. The granules passed from 22 # sieve & retained on 44 # sieve were used for tabletting. 10% of fines of the total weight of granules were mixed with retained granules. Weighed quantity of lubricant & glidant were mixed with granules at last. Finally the blend was compressed using 9.5 mm flat punch to an average weight of 400 mg using Rimek RSB-4 Minipress.

Weight variation test[8]

Twenty tablets were weighed individually, average weight was calculated & individual tablet weights were compared to the average weight. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit & if no tablet differs by more than two times the percentage limit.

Hardness[9]

The tablet hardness is defined as the force required breaking a tablet in a diametric compression test. To perform this test, a tablet is placed between two anvils, force is applied to the anvils & the crushing strength that just causes the tablet to break is recorded. The hardness was measured using Monsanto tester. It is expressed in Kg/cm^2.

In vitro Buoyancy[10]

The tablets were placed in 100 ml beaker containing 0.1 N HCl. The medium was kept in stagnant condition & the temperature was maintained at 37^oC. The time required for the tablet to rise to the surface of the medium was determined as *in vitro* buoyancy.

Floating Time

If the tablet floated at the surface of the medium for prolonged period of time, it was determined as floating time.

Table 1: Weight variation tolerances for uncoated tablets

Average weight of tablets (mg)	Maximum percentage difference allowed
130 or less	10
130-324	7.5
More than 324	5

Table 2: Formulation of dummy tablets using Psyllium Husk as Natural Polymer

Ingredients	T1 (%)	T2 (%)	T18 (%)	T19 (%)	T20 (%)
HPMC K4M	25	-	29.62	28	30
HPMC E4M	-	25	-	-	-
Psyllium Husk	**7**	**9**	**14.81**	**14**	**10**
$NaHCO_3$	18	17	3.7	18	15
Citric Acid	18	17	3.7	18	15
Mg. Stearate	2.5	2.5	1	1	1
Talc	2	2	1	1	1
MCC	13.75	13.75	23.08	10	14
Sp. Dr. Lactose	13.75	13.75	23.08	10	14

Table 3: Formulation of dummy tablets using Psyllium Husk as Natural Polymer

Ingredients	PH1 (%)	PH2 (%)	PH3 (%)	PH4 (%)
HPMC K4M	28	28	28	28
Psyllium Husk	**10**	**14**	**18**	**22**
$NaHCO_3$	18	18	18	18
Citric Acid	18	18	18	18
Mg. Stearate	1	1	1	1
Talc	1	1	1	1
MCC	24	20	16	12

Table 4: Formulation of dummy tablets using Tara Gum as Natural Polymer

Ingredients	T5 (%)	T6 (%)	T7 (%)	T16 (%)	T17 (%)
HPMC K4M	-	30	-	30	20
Tara Gum	**30**	**30**	**40**	**20**	**20**
$NaHCO_3$	18	9	18	15	18
Citric Acid	18	9	18	15	18
Mg. Stearate	2.5	2.5	3	1	1
Talc	2	2	1	1	1
MCC	14.75	8.75	10	9	11
Sp. Dr. Lactose	14.75	8.75	10	9	11

Table 5: Formulation of dummy tablets using Tara Gum as Natural Polymer

Ingredients	TG1 (%)	TG2 (%)	TG3 (%)	TG4 (%)
HPMC K4M	20	20	20	20
Tara Gum	**15**	**20**	**25**	**30**
$NaHCO_3$	18	18	18	18
Citric Acid	18	18	18	18
Mg. Stearate	1	1	1	1
Talc	1	1	1	1
MCC	27	22	17	12
Sp. Dr. Lactose	-	-	-	-

Table 6: Formulation of dummy tablets using Gellan Gum

Ingredients	T3 (%)	T4 (%)
HPMC K4M	-	-
HPMC E4M	-	21
NaCMC	**31.25**	-
Gellan Gum	**31.25**	**42**
$CaCO_3$	**10**	-
Citric Acid	**3**	**5**
$CaCl_2$	-	**10**
Mg. Stearate	1	1
Talc	1	1
MCC	11.25	10
Sp. Dr. Lactose	11.25	10

Table 7: Formulation of dummy tablets using Gellan Gum

Ingredients	T8 (%)	T9 (%)	T10 (%)	T11 (%)	T12 (%)
HPMC K4M	30	35	35	30	35
Gellan Gum	**0.5**	**0.5**	**0.5**	**0.5**	**10**
$CaCO_3$	**0.5**	**1**	**2**	**3**	**10**
Sodium Citrate	**0.5**	**1**	**2**	**3**	**10**
Mg. Stearate	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5
MCC	32.75	29.75	28.75	30.25	16
Sp. Dr. Lactose	32.75	29.75	28.75	30.25	16

Table 8: Formulation of dummy tablets using Gellan Gum

Ingredients	T13 (%)	T14 (%)	T15 (%)
HPMC K4M	30	30	30
Gellan Gum	**1**	**1**	**3**
$NaHCO_3$	**0.4**	**0.4**	**0.4**
$CaCl_2$	**3**	**4**	**5**
Mg. Stearate	1.5	1.5	1.5
Talc	1.5	1.5	1.5
MCC	31.3	30.8	29.3
Sp. Dr. Lactose	31.3	30.8	29.3

Table 9: Formulation of dummy tablets using Gellan Gum

Ingredients	12A (%)	12B (%)	12C (%)
HPMC K4M	35	35	35
Gellan Gum	**10**	**10**	**10**
$CaCO_3$	**14**	**18**	**22**
Sodium Citrate	**14**	**18**	**22**
Mg. Stearate	1	1	1
Talc	1	1	1
MCC	25	17	9

RESULT

Table 2 (A)

Parameters	T5	T6	T7	T16	T17
Wt. Variation (gm)	0.39 ± 0	0.36 ±0.005	0.39 ± 0.005	0.39 ± 0.005	0.39 ± 0
Hardness (Kg/Cm^2)	1.95 ± 0.60	1.66 ± 0.72	2.01 ± 0.66	2.53 ± 0.46	1 ± 0
In vitro Buoyancy (Sec)	195.3 ± 27.50	539.3 ± 1.15	1800 ± 0	1280 ± 173.2	1320 ± 0
Floating Time (hrs)	0.053 ± 0.007	36 ± 0	37 ± 0	24 ± 0	21 ± 0

Table 3 (A)

Parameters	T1	T2	T18	T19	T20
Wt. Variation (gm)	0.38 ± 0.01	0.39 ± 0.01	0.39 ± 0.005	0.4 ± 0	0.39 ± 0
Hardness (Kg/Cm^2)	2 ± 0	2 ± 0	2.7 ± 0.17	1.16 ± 0.14	1.66 ± 0.28
In vitro Buoyancy (Sec)	**8 ± 0**	8.1 ± 1.15	4075 ± 5	**8.3 ± 0.57**	**21 ± 1.7**
Floating Time (hrs)	**24 ± 0**	0.16 ± 0.005	-	**24 ± 0**	**20 ± 0**

Table 4 (A)

Parameters	TG1	TG2	TG3	TG4
Wt. Variation (gm)	0.39 ± 0	0.39 ± 0.005	0.39 ± 0.005	0.39 ± 0.005
Hardness (Kg/Cm^2)	1.2 ± 0	1 ± 0	0.86 ± 0.11	0.86 ± 0.11
In vitro Buoyancy (Sec)	3440 ± 557.4	2440 ± 34.64	1360 ± 399.4	20 ± 7.07
Floating Time (hrs)	24 ± 0	24 ± 0	24 ± 0	24 ± 0

Table 5 (A)

Parameters	PH1	PH2	PH3	PH4
Wt. Variation (gm)	0.38 ± 0.005	0.39 ± 0	0.4 ± 0	0.4 ± 0
Hardness (Kg/Cm^2)	2.5 ± 0	2 ± 0	1.2 ± 0	1.2 ± 0
In vitro Buoyancy (Sec)	20 ± 1.73	16 ± 1	15 ± 2	14.66 ± 1.52
Floating Time (hrs)	0.24 ± 0.005	19 ± 0	24 ± 0	24 ± 0

Table 6 (A)

Parameters	T3	T4
Wt. Variation (gm)	0.38 ± 0	0.36 ± 0.01
Hardness (Kg/Cm^2)	2 ± 0	2 ± 0
In vitro Buoyancy (Sec)	598 ± 2	118.6 ± 12.0
Floating Time (hrs)	1 ± 0	0.16 ± 0.005

Table 7 (A)

Parameters	T8	T9	T10	T11	T12
Wt. Variation (gm)	0.38 ± 0.005	0.38 ± 0	0.39 ± 0	0.39 ± 0.005	0.39 ± 0
Hardness (Kg/Cm^2)	4.2 ± 0	4.73 ± 0.46	4.2 ± 0	4 ± 0	4.16 ± 0.35
In vitro Buoyancy (Sec)	-	-	-	-	1260 ± 1158.7
Floating Time (hrs)	-	-	-	-	24 ± 0

Table 8 (A)

Parameters	T13	T14	T15
Wt. Variation (gm)	0.39 ± 0.01	0.39 ± 0	0.39 ± 0.005
Hardness (Kg/Cm^2)	4.2 ± 0	4.73 ± 0.46	4.06 ± 0.23
In vitro Buoyancy (Sec)	-	-	-
Floating Time (hrs)	-	-	-

Table 9 (A)

Parameters	12A	12B	12C
Wt. Variation (gm)	0.39 ± 0.005	0.39 ± 0.005	0.39 ± 0.005
Hardness (Kg/Cm^2)	4.33 ± 0.76	3.86 ± 0.11	3.7 ± 0.17
In vitro Buoyancy (Sec)	660 ± 216.3	1700 ± 124.8	2660 ± 307.8
Floating Time (hrs)	24 ± 0	24 ± 0	24 ± 0

DISCUSSION

In the initial trial i.e. T1 when HPMC K4M (25%) was used in the combination with psyllium husk (7%), the least lag time of 8 second, floating time of 24 hrs & hardness of 2 Kg/Cm^2. Still in an attempt to optimize the concentration of psyllium husk & HPMC K4M on trial & error method, few more trials were performed using this combination. From the trials PH2, PH3 & PH4, it was found that as the concentration of psyllium husk was increased, lag time was found to decrease. Decrease in lag time may also be attributed to the presence of effervescent agents (citric acid: sodium bicarbonate) in the ratio of 18:18. Citric acid caused rapid formation & entrapment of CO_2 gas into the hydrophilic polymeric gel. [3] Increase in the floating time may be attributed to the increase in the concentration of HPMC K4M. HPMC K4M hydrate rapidly only at the surface, retaining their original air bubbles & extending floatation beyond 8 hrs.[11] Tablet hardness was compromised in all cases of the formulation containing psyllium husk which may be because psyllium husk is a natural superdisintegrant.[12] (Table: 2, 3, 2(A), 3(A)).

Another attempt was made to develop the formulations containing the combination of tara gum & HPMC K4M. The formulations containing only tara gum i.e. T5 & T7 were found show poor floating time as well as lag time respectively. The floating time of 0.053 ± 0.007 hrs in T5 may be attributed to the absence of HPMC K4M as it helps in entrapment of CO_2 bubbles. Lag time of 1800 sec may be attributed to the absence of HPMC K4M & floating time of 37 hrs in T7 may be due to presence of 40% of tara gum. As further trials were carried out in an attempt to improve the lag time & floating time, TG4 showed comparatively very good result of 20 ± 7.07 sec lag time & 24 hrs floating time. This may be attributed 1st of to the combination of both the tara gum & HPMC K4M. Secondly, may be due to 20:30 ratio of HPMC K4M:Tara gum. In all the case, once again hardness was compromised which may be due to the presence of tara gum. (Table: 4, 5, 4 (A), 5 (A)).

One another attempt was made to develop the formulations with the combination of Gellan gum & HPMC K4M. Approximately, 13 formulations were prepared on trial & error method to find out the exact excipients for the tablet formulation. The extra excipients include sodium carboxy methyl cellulose, calcium carbonate, calcium chloride, sodium citrate. Sodium carbonate was tried only in 3 formulations (T13 – T15) as it was insisted by DR Bhimani et al that on increasing the calcium carbonate concentration, the lag time was reduced & floating was increased.[13] In the 1st two formulations i.e. T3 & T4 (Table: 6, 6 (A)), Gellan gum alone was used with the absence of HPMC K4M. Hence, may be hardness, lag time & floating time were compromised. When the concentration of calcium carbonate & sodium citrate was used in very less proportion along with very less concentration ratio of Gellan gum: HPMC K4M, all the tablets sank & none of them

floated (formulations T8 – T11) (Table: 7, 7 (A)). As the concentration of calcium carbonate & sodium citrate was increased up to 10:10 & the concentration of Gellan gum: HPMC K4M was increased up to 10:35, at least 1260 ± 1158.7 sec of buoyancy & 24 hrs of floating time was achieved in the formulation T12 which was comparatively good. In an attempt to improve the buoyancy, 0.4% of sodium bicarbonate was incorporated in formulations from T13 – T15 as insisted by Anurag Verma & JK Pandit.[14] But still the tablets did not float at all which may be due to the difference in the concentration of Gellan gum & HPMC K4M (Table: 8, 8 (A)). Based on the result of T12, further trials were carried out where 12A showed still better result of 660 ± 216.3 sec buoyancy & 24 hrs of floating time which may be attributed to higher concentration ratio of calcium carbonate: sodium citrate of 14:14. Further increase in the concentration of calcium carbonate: sodium citrate, lag time was compromised. (Table: 9, 9(A)). Hardness of all the formulations was found to be excellent which may be due to combination of Gellan gum & HPMC K4M except for the T3 & T4. Among all the formulations containing Gellan gum, T12 & 12A were found to be the best formulations. Further trials will be focused on how to improve the hardness of tablet formulations containing psyllium husk & tara gum. The future idea is gellan gum can itself be used as a binder or acacia mucilage, tragacanth mucilage; gelatine or starch paste can be used to improve the hardness of tablet formulations.

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