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Development and evaluation of novel immediate release tablets of Metoclopramide HCl by direct compression using treated gellan gum as a disintegration-accelerating agent.

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ABSTRACT

The aim of this study was to compare the disintegrants efficiency of the three superdisintegrants (Ac-Di-Sol, Polyplasdone XL and Explotab) and also to compare disintegrant properties and disintegrant efficiency of agar (AG) and gellan gum (GG) with treated agar (TAG) and treated gellan gum (TGG) by formulating metoclopramide HCl immediate release tablets by direct compression method. In the present investigation, we have attempted first time report on TGG as disintegrant. Disintegration efficiency of powder disintegrants compared by swelling & hydration capacity of disintegrants. While efficiency of disintegrants in tablets compared by various test like disintegration time, dissolution test, wetting time & maximal water uptake study of metoclopramide HCl immediate release tablets. The rapid disintegration observed for the TAG and TGG containing tablets due to high-porous structure of treated form of disintegrants which confirmed by photomicroscope study. Comparing three classes of superdisintegrants represented by Ac-Di-Sol, Polyplasdone XL and Explotab with AG, TAG, GG and TGG. The treated form of disintegrants (TAG, TGG) in which TAG was found to be more effective than TGG. The disintegration efficiency was found in following decreasing order Ac-Di-Sol, Explotab, Polyplasdone XL, TAG, TGG, AG and GG.

Keywords: Immediate release tablet, treated gellan gum, disintegration.

INTRODUCTION

To enhance dissolution and hence bioavailability of any drug from immediate release tablets, disintegration is one of the important process. Few Super-disintegrants are available commercially but due to the cost and expanding need of market, development of new disintegrants is required.

In the present investigation, we tried to judge the disintegration efficiency of disintegrants by comparing various parameters such as disintegration time, wetting time, maximal water uptake capacity and dissolution study of tablet. Disintegrants powder properties like swelling and hydration capacity was compared.

Various techniques can be used to formulate immediate release tablets[1]. Direct compression, is one of the techniques that requires the incorporation of a superdisintegrant into the formulation. Direct compression does not require the use of water or heat during the formulation procedure and is very sensitive to changes in the type and proportion of excipients and the compression forces, when used to achieve tablets of suitable hardness without compromising the rapid disintegration characteristics.

Recently, immediate release tablets have gained prominence of being new drug delivery systems.[2] Most immediate release tablets are intended to disintegrate in the stomach, where the pH is acidic.[2] The objective of this article was to investigate the novel disintegrants and it's comparison with reported superdisintegrants in simulated gastric fluid and their efficiency in promoting disintegration and dissolution of active ingredients from directly compressed tablets of metoclopramide HCl.

Gellan gum (GG) is a linear anionic polysaccharide, biodegradable polymer obtained from *Pseudomonos elodea* consisting of a linear tetrasaccharide repeat structure and used as a food additive. Agar (AG) is the dried gelatinous substance obtained from *Gelidium amansii* (Gelidanceae) and several other species of red algae like, *Gracilaria* (Gracilariaceae) and *Pterocadia* (Gelidaceae). Both were reported earlier as disintegrant.[3] TAG has better disintegration efficiency than AG.[4] Same procedure was adopted for to enhance disintegrant efficiency to GG.

MATERIALS AND METHODS

Materials

Metoclopramide HCl (260 µm) was obtained as a gift sample from Ipca Laboratory (Mumbai, India). Ac-Di-Sol (NMT 2 % retained # 200, NMT 10 % retained # 325) and Polyplasdone XL (<400 µm) were obtained from Wockhardt Research Centre (Aurangabad, India). Explotab (35-55 µm) and microcrystalline cellulose (50 µm) were obtained as a gift samples from JRS Pharma (USA). Agar (671 µm) was obtained as a gift sample from Marine chemical (Mumbai, India), Gellan gum (355 µm) was obtained as a gift sample from Burzin and Leons (Mumbai, India). Magnesium stearate and colloidal silicone-dioxide were obtained from S.D.Fines (Mumbai, India).

Methods

TAG and TGG powders were prepared by taking 10 g (AG, GG) powder separately with sufficient distilled water (100 ml) and allowed to swell

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for 1 day at controlled room temperature. Then spread with mechanically in petri-dish and allowed for drying up to 3 days in incubator at 37 ± 1 ^{0}C and then pulverized by pulveriser (D.P.Pulverized industries, Mumbai).

Powder Characterization:

1. Particle size distribution

The measurement of particle size distribution was performed by sieving method using a vibration sieve apparatus (Remik, Karnavati engineering Ltd., Ahmedabad, India).[4]

2. Photo-microscope study

Photo-microscope image of TGG and GG was taken at 450 magnifications by photomicroscope (Motic B1 series microscope, Japan).[4]

3. Angle of repose

The angle of repose of disintegrants was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and the angle of repose was calculated using the following equation.[5]

$\tan(\theta) = h/r$……..… (1)

where *h* and *r* are the height and radius of the powder cone.

4. Moisture sorption capacity

All disintegrants have capacity to absorb moisture from atmosphere which affects moisture sensitive drug. So moisture sorption capacity was performed by taking 1 g of each disintegrants were uniformly distributed in petri-dish. Then kept in stability chamber (Programmable environmental test chamber, Remi) at 37 ± 1 ^{0}C and 100 % Relative humidity for 2 days and investigated amount of moisture uptake by difference between weights.[5]

5. Density

The loose bulk density (LBD) and tapped bulk density (TBD) were determined. Disintegrant (2 g) was introduced into a 10-mL calibrated measuring cylinder. After the noting down the initial volume, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas.[5,6]

LBD=weight of the powder/volume of the packing… …… ..… (2)

TBD = weight of the powder/tapped volume of the packing… ... (3)

6. Compressibility

The compressibility index of the granules was determined by Carr's compressibility index.[5,6]

Carr's index = (TBD – LBD) 100/TBD……..… (4)

7. Swelling capacity

The swelling capacity of disintegrants were measured by taking 1 gm disintegrant was added to 10 ml simulated gastric fluid. The measuring cylinder was shaken vigorously for 10 minutes and allowed to stand for 24 hrs at 37 ± 1 ^{0}C. Swelling capacity was expressed as percentage and calculated according to the equation.[7, 8, 9]

Swelling capacity = (Xv/Xi) 100……. (5)

Where, Xv = Final volume occupied by swollen material after 24 hrs.

Xi = Initial volume of the powder in measuring cylinder.

8. Hydration capacity

Disintegrant (1 g) was taken in to 15 ml tarred centrifuge tube and 10 ml of simulated gastric fluid was added and allowed to stand for 10 minutes. During this time interval the content was mixed by inverting the tubes. After removal of the tubes supernatant was carefully decanted and tubes were inverted to allow drain. The tubes were then weighed in digital balance (Shimadzu) and the hydration capacity was calculated according to following formula.[7, 8, 9]

Hydration capacity = weight of hydrated sample / dry sample weight…… (6)

9. Drug–Excipient Interaction Study [13]

Thin Layer Chromatography

Physical mixture of drug and excipient was filled in the clean ampules and sealed. The sealed ampules were kept at 37±0.5 °C and 75% RH for 28 days in stability chamber. Then Rf values of plain drug, excipient and their mixture were determined. Mobile phases for MTH (methanol: ammonia [1.5: 0.2]) was used. Aluminium backed silica gel 60 F254 HPTLC plates (10×20 cm, layer thickness 0.2 mm, E-Merck, Darmstad, Germany) prewashed with methanol was used for the study.

DSC Study

Thermograms of MTH and immediate release layer were performed using DSC (Perkin Elmer Cyris-DSC). Indium was used as standard to calibrate the DSC temperature and enthalpy scale. The sample were hermetically sealed in aluminum pans and heated at a constant rate of 10°C/min over a temperature range of 50–200°C.

Preparation of tablets

Metoclopramide HCl and microcrystalline cellulose (MCC) were mixed with disintegrant for 15 minutes in porcelain mortar, passed through 60 # sieve. This blend was mixed with colloidal silicon-dioxide and magnesium stearate for 5 minutes and processed for direct compression by using 7 mm round flat-faced punch of rotary tablet machine (Karnavati, India). Compression force was kept constant for all formulations. The magnesium stearate level was fixed at 2 % for all formulation. Disintegrants were used at 8 % in tablets.

Evaluation of immediate release tablets

1. Weight variation, drug content, friability, hardness and thickness

Tablet weight variation, thickness and friability were measured using the USP methods and criteria. It has been reported that metoclopramide HCl can be detected at 273 & 305 nm. Drug content uniformity of MTH was carried out at 305 nm because successive extraction was done using chloroform for which good absorption observed at 305 nm as reported in Pharmacopoeia. During dissolution test study, metoclopramide HCl shown good absorption at 273 nm by using pH 1.2 HCl buffer solution as a dissolution media. Tablet friability was measured using friability tester (Roche friabilator). Thickness was measured by vernier caliper and hardness of tablet was measured by Monsanto hardness tester. Weight, drug content, hardness and thickness of tablet were representing as mean ± SD.

2. Disintegration test

Randomly six tablets were selected from each batch for disintegration test. Disintegration test was performed without disc in simulated gastric fluid using USP disintegration apparatus. The mean ± SD of 6 tablets were calculated.[10]

3. Dissolution test

Dissolution test of metoclopramide HCl tablets was performed using simulated gastric fluid with USP dissolution apparatus 2 at 50 rpm and

Table 1. Particle Size Distribution of GG and TGG.

Size (mesh)	GG(% weight)	TGG (% weight)
20/40	0	8.60
40/60	1.15	23.00
60/100	20.10	32.53
100 pass	78.75	35.87

Figure 1. Photomicroscope image of gellan gum powder

Figure 2. Photomicroscope image of treated gellan gum powder

Table 2. Powder Properties of GG and TGG.

Disintegrants	Angle of repose	LBD (g/ml)	TBD (g/ml)	Compressibility index (%)	Loss on drying(%)	Moisture Absorption Capacity per g
GG	27.34	0.55	0.62	11.12	11.8	0.085
TGG	10.78	0.31	0.45	31.24	7.8	0.026

Figure 3.Disintegration time of MTH tablets (Batch F1-f7)

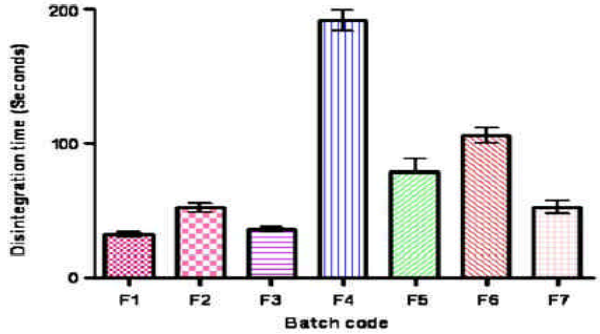

Table 3. Disintegrants Powder Properties*

Disintegrants	Swelling Capacity (%)	Hydration capacity (g water/g polymer)
Ac-Di-Sol	602.38(8.25)	8.92(0.00)
Polyplasdone XL	161.67(10.41)	4.47(0.02)
Explotab	559.63(25.82)	7.88(0.30)
GG	345.00(14.75)	5.94(0.23)
TGG	407.50(26.10)	7.00(0.00)
AG	378.33(7.64)	6.06(0.05)
TAG	420.17(8.80)	7.03(0.11)

** All Values are mean ± SD, (n = 3)*

Table 4. Composition of the Metoclopramide HCl tablet*

Ingredient	F1	F2	F3	F4	F5	F6	F7
Metoclopramide HCl	10	10	10	10	10	10	10
Ac-Di-Sol	08	-	-	-	-	-	-
Polyplasdone XL	-	08	-	-	-	-	-
Explotab	-	-	08	-	-	-	-
GG	-	-	-	08	-	-	-
TGG	-	-	-	-	08	-	-
AG	-	-	-	-	-	08	-
TAG	-	-	-	-	-	-	08
MCC	80	80	80	80	80	80	80
Magnesium stearate	01	01	01	01	01	01	01
Colloidal silicon-dioxide	01	01	01	01	01	01	01

** All values are in mg.*

Figure 4. Dissolution study of Metoclopramide HCl tablet

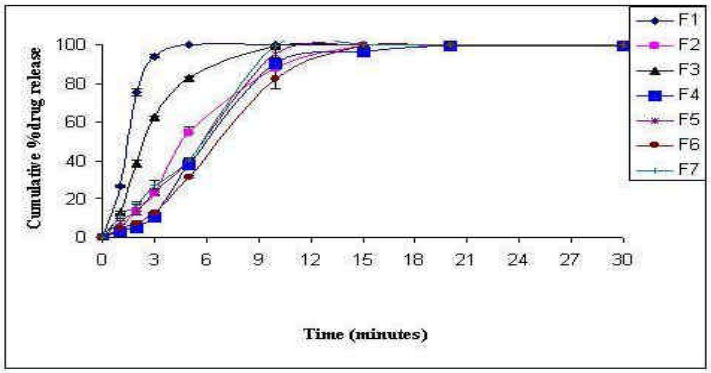

Table 5. Evaluation of Immediate release Metoclopramide HCl Tablet

Batch	Weight* (mg)	Thickness* (mm)	Hardness* (Kg/cm^2)	Friability† (%)	Disintegration time*(Seconds)	Drug content* (%)
F1	101.0(1.4)	2.24(0.05)	4.50(0.00)	0.33	32.33(5.53)	99.9(1.38)
F2	101.4(1.2)	2.30(0.00)	5.00(0.49)	0.19	52.16(12.98)	101.4(0.87)
F3	99.2(1.68)	2.23(0.04)	4.00(0.00)	0.64	35.66(4.58)	101.2(0.84)
F4	100.8(1.2)	2.17(0.04)	4.75(0.35)	0.29	191.5(31.23)	99.7(2.08)
F5	99.9(1.21)	2.24(0.05)	4.10(0.00)	0.37	78.66(22.34)	101.3(1.28)
F6	100.2(1.0)	2.19(0.03)	4.90(0.14)	0.58	105.8(14.16)	101.2(0.84)
F7	100.1(1.3)	2.27(0.04)	3.90(0.14)	0.74	52.50(12.27)	102.2(0.80)

** All values are mean ± SD, (n = 6) ;† All values are singly measured.*

Table 6. Metoclopramide HCl tablets properties*

Batch	$Q_{1min.}$(%)	$Q_{3min.}$(%)	$Q_{5min.}$(%)	Wetting time (seconds)	Maximal water uptake(mg/tablet)
F1	26.35(0.00)	94.16(0.91)	99.95(0.25)	40.66(1.52)	395.00(7.55)
F2	5.01(0.11)	22.68(0.78)	54.69(2.69)	35.33(3.05)	238.33(7.64)
F3	12.83(0.64)	62.51(1.21)	82.95(1.36)	52.00(2.00)	366.33(14.57)
F4	3.91(0.64)	10.74(1.93)	37.79(2.23)	224.33(8.64)	238.33(7.63)
F5	7.90(0.92)	23.54(1.55)	40.58(0.65)	175.00(8.14)	339.33(47.64)
F6	4.93(0.39)	12.70(0.54)	31.09(0.64)	532.00(52.02)	312.36(74.95)
F7	10.88(0.82)	27.12(2.27)	40.69(1.29)	161.00(10.50)	346.00(18.58)

**All values are mean ± SD, (n = 3).*

Figure 5. Wetting study of Metoclopramide HCl tablet

37 ± 0.5 ^{0}C temperature. Test sample (5 ml) was withdrawn at particular time interval (1, 2, 5, 10, 15, 20 and 30 minutes) and replaced with fresh dissolution media maintained at 37 ± 0.5 ^{0}C. The test sample was filtered (membrane filter, 0.45 µm) and the concentration of drug determined using UV spectrophotometer at λ_{max} 273 nm. This test was performed on 3 tablets and mean ± SD calculated.

4. Wetting time

The tablet was placed at the centre of 2 layers of absorbent paper fitted in to petri-dish. The absorbent paper was thoroughly wetted with simulated gastric fluid, excess fluid was completely drained out of the petri-dish. The time required for the fluid to diffuse from the wetted absorbent paper into the entire tablet was recorded using a stopwatch. This test was performed in triplicate and mean ± SD calculated. [11]

5. Maximal water uptake capacity

Modified method and apparatus was used for the water uptake study.[12] The apparatus consists of a sample holder and a liquid holding vessel (petri-dish), set on an electronic digital balance. When tablet was placed onto sample holder, then fluid was passively withdrawn in to the tablet. The loss of weight from the liquid holder was read from the digital balance. Test was performed in triplicate. All results were reported as mean ± SD.

RESULTS AND DISCUSSION

Particle Size Distribution

Particle size distribution of GG and TGG were found different as represented in Table 1. Particles retained over 100 # sieve was 21 % and 64 % for TGG and GG. Water treatment produces coarse particle in TGG than GG. Particle size is one of the factor that affects disintegration activity.[3] A larger particle size and hence, increased porosity leads to a faster wicking and swelling of disintegrants.[9] Larger particle size probably yielded greater pore size and altered the shape of the pore.[3]

Photomicroscope Study

Coarse particle of TGG also confirmed by photomicroscope image as shown in Figure 1 and 2 for GG and TGG respectively. Larger particles of disintegrants swelled more rapidly and to a greater extent than did the smaller particle.[3] TGG had taken less time for disintegration of tablet than GG containing tablet. Same results were found in case of AG and TAG.[4]

Angle of Repose, Moisture Sorption Capacity, Density and Compressibility

Powder properties like compressibility index, angle of repose, loss on drying, bulk density (LBD, TBD) and moisture absorption capacity represented in Table 2. Bulk density of TGG was found to be less than GG (TGG = 0.31 g/ml, GG = 0.55 g/ml) that indicates more porous structure of TGG than GG. Therefore, tablets prepared from TGG had faster wicking and swelling then GG and hence faster disintegration of tablets containing TGG as compared to GG.

Swelling and Hydration Capacity

Swelling and hydration capacity of disintegrants are the important parameters for comparing disintegration efficiency represented in Table 3. Higher swelling and hydration capacity (capability of absorbing water) of Ac-Di-Sol leads to faster disintegration of batch F1 (32.33 ± 5.53 seconds). Higher Swelling and hydration capacity of TGG and TAG leads to faster disintegration than GG and AG. Less swelling capacity of polyplasdone XL than AG, GG, TAG and TGG but disintegration was found to be faster than AG, GG, TAG and TGG because the capillary activity of polyplasdone XL for water is responsible for its tablet fast disintegration.[2] Explotab was found to be less swelling capacity than Ac-Di-Sol and it was found to be more effective then polyplasdone XL.

Drug–Excipient Interaction Study

The results of TLC study indicate no change in the Rf value of drugs and no interaction between drug and excipient. DSC study demonstrate, there is no change in the melting point of drug (MTH=183 °C) which shows that no drug–excipient interaction.

Evaluation of Tablet

Tablets prepared from GG and AG were found to thinner and harder than tablet prepared from TGG and TAG. Hardness of batch F2 was found to be higher than remaining formulation because binder property of ploysplasdone XL.[1] Results of hardness and thickness measurements shows that the TAG and TGG were harder to make compact than the AG and GG. Properties of all tablets are represented in Table 5.

Disintegration and dissolution test of all batches were performed in simulated gastric fluid represent that Ac-Di-Sol was found to be best among all disintegrants which confirms the earlier report.[2] TGG and TAG containing tablets were found to disintegrate faster that GG and AG containing tablets. Disintegration time for all batches shown in Table 5. Cumulative % of drug released at 1, 3 and 5 minutes represents as $Q_{1min,}$ Q_{3min} and Q_{5min} to check positive correlation between the maximal water uptake and the cumulative % of drug dissolved at 1, 3 and 5 minutes shown in Table 6 TGG and TAG containing tablets showed faster disintegration. Cumulative % drug release versus time plot of all batches shown in Figure 3.

Wetting time of all batches represented in Tablet 6. Faster wetting occur of batch F2 containing polyplasdone XL because it shows disintegration of tablet by capillary mechanism.[1] Wetting time of tablet was in following decreasing order polyplasdone XL, Ac-Di-Sol, Explotab, TAG, TGG, AG and GG. The comparative wetting time data of GG, TGG, AG and TAG containing tablets shown in Figure 4. Maximal water uptake of all batches shown in Table 6. Higher water uptake leads to faster disintegration and dissolution of tablets. Ac-Di-Sol was found to best among all disintegrants.

CONCLUSIONS

GG and AG are less effective disintegrants compared to TGG and TAG. TGG holding a potential as a disintegrants. Among the all disintegrants, Ac-Di-Sol was found to be more effective. High swelling capacity of Ac-Di-Sol among all disintegrants make it more effective than all other disintegrants.

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