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Modified Polysaccharides as Fast Disintegrating Excipients for Orally Disintegrating Tablets of Fexofenadine HCl

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ABSTRACT

In the present study comparisons of natural and synthetic superdisintegrants were performed. The purpose of this study was to develop a dosage form that was easy to administer and provides rapid release of the drug Fexofenadine HCL using Treated agar and modified treated agar (co-grinded agar) as rapidly disintegrating excipients. Modified co-grinded treated agar (C-TAG) was prepared by subjecting pure polysaccharides namely agar to sequential processes of wetting, drying and co grinding with mannitol (1:1). Their disintegrating and physiochemical properties were evaluated and compared with synthetic superdisintegrant Crosspovidone. The modified polysaccharide was characterized by Scanning Electron Microscopy and evaluated for particle size distribution, derived properties, swelling index and biodegradability. The orally disintegrating Tablets (ODT) were prepared by direct compression method using microcrystalline cellulose and Mannitol as direct compressible vehicle. These tablets were evaluated for quality control tests like Organoleptic characteristics, weight variation, hardness, friability, in-vitro disintegration time, in-vitro swelling time, drug content and dissolution behavior. Among all the superdisintegrants, Modified co-grinded treated agar showed the highest swelling index. Hence, the present study revealed that this natural superdisintegrants (Modified co-grinded treated agar) showed similar disintegrating property than the most widely used synthetic superdisintegrants in the formulations of ODT.

Key Words: Fexofenadine HCL, Modified co-grinded treated agar, Crosspovidone,

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INTRODUCTION

Orally disintegrating tablets (ODTs) are often prescribed for older people and children whose swallowing abilities are poor, as they disintegrate easily in saliva in the mouth without the need for additional water [1].Recently, ODT formulations have been developed for various medicines, and many generic products are now available on the market. When ODTs disintegrate in the mouth, the concentration of dissolved drug in the mouth is greater than that which is found when conventional tablets are kept in the mouth. Currently available technologies for manufacture of orally disintegrating tablets can be broadly classified into two major categories namely conventional and patented technologies. Most of the technologies require specialized processing conditions and equipments except for some conventional cost effective technologies like direct compression and disintegrant addition [2]. Disintegrant addition is one of the popular techniques for formulating orally disintegrating tablets whereby optimum concentrations of superdisintegrants are added to the formulation to achieve rapid disintegration accompanied with good mouth feel. Numerous literature reports suggest the use of relatively expensive semi synthetic polymeric superdisintegrants like Crosspovidone, croscarmellose sodium, sodium starch glycollate, PVPK12 and cross linked sodium carboxy methylcellulose [3] The reports on use of natural polysaccharides like treated agar and guar gum as disintegrants for rapidly disintegrating tablets are relatively fewer. The present study was aimed to modify selected polysaccharides by simple techniques, characterize, and assess their orally disintegrating properties by formulating and evaluating orally disintegrating tablets of the model drug. Fexofenadine HCl. Presumed mechanism of disintegration is that, the porous nature of the modified polysaccharides shall facilitate water absorption, thereby causing swelling of polysaccharides without forming gelatinous mass in water, which may lead to excellent disintegration of tablet. Fexofenadine HCl, is a non-sedating anti histamine used in the symptomatic relief of allergic conditions including seasonal allergic rhinitis and urticaria. An orally disintegrating tablet of Fexofenadine HCl. may provide a dosage form that is easy to administer, provide rapid release of drug and also enhance bioavailability of the drug by pregastric absorption through mouth, pharynx and oesophagus, as the drug releases in saliva and passes down in to the stomach.

MATERIALS AND METHODS

Fexofenadine HCL was supplied as gift sample by Cadila Pharmaceutical ltd. Ahemdabad India. Agar purchased from CDH. Mannitol and M.C.C was supplied as gift sample by Signet Chemical Pvt. Ltd. Mumbai.

Preparation of treated agar (TAG):

Suitable quantity of Agar powder (5-10g) weighed and added in distilled water (100ml). Agitation was done continuously by a stirrer for one day to swell the contents. The swollen contents were dried on a tray for 3 days at room temperature. The dried powders were grinded by mortar and pestle. Then grinded powder was passed through sieve no.100.

Preparation of co-grinded TAG

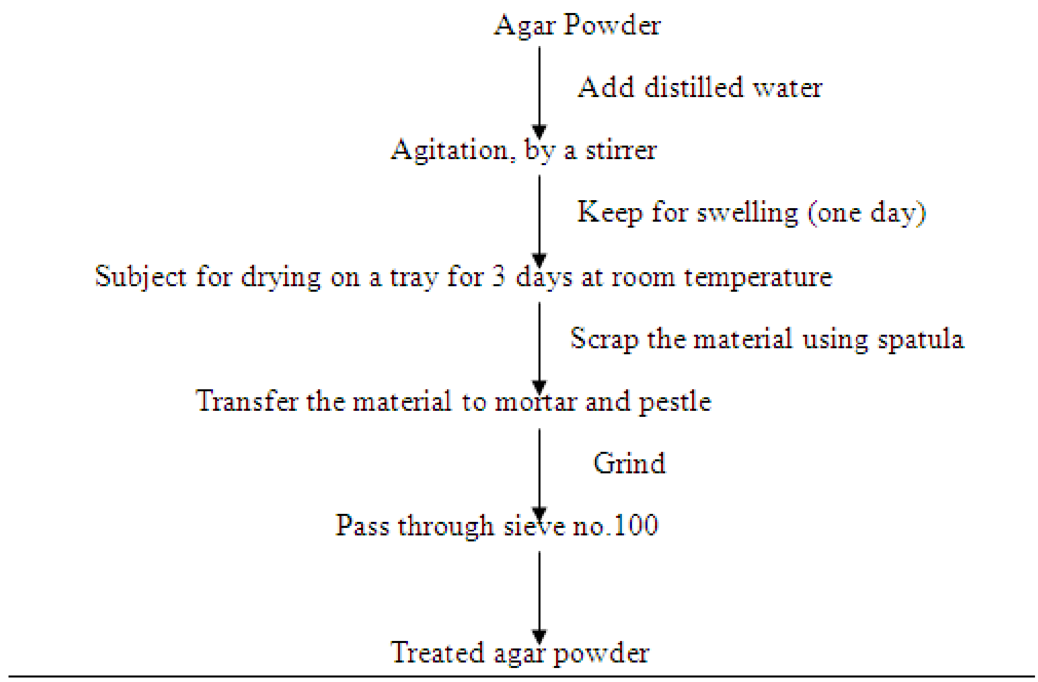
Treated polysaccharides was then co-grinded with Mannitol (1:1) in a glass pestle mortar for 20 min and passed through sieve (# 22) to get the modified polysaccharides—co-grinded treated agar (C-TAG).

Preformulation characterization of superdisintegrants.

The superdisintegrants were evaluated for their physicochemical properties. The particle size was characterized by using SEM studies. **Fig.1** Particle size distribution studies for pure, treated and modified polysaccharides were carried out by the method of sieving and microscopic method. The mass volume relationship and flow properties were determine for their compressibility property [4].

Preparation of Modified Polysaccharides as Fast Disintegrating Excipients

Preparation of treated Agar (TAG)



Evaluation of Derived Properties

The derived properties of pure, treated and modified polysaccharides were obtained using bulk density apparatus and the obtained values of loose bulk and tapped bulk densities were subjected to the calculation of Carr's index and Hausner ratio [5].

Swelling Capacity/ Swelling Index

Disintegrant (1gm) was taken in the measuring cylinder. Then distilled water (10ml) was poured in it. The measuring cylinder was shacked vigorously for 10min. and allowed to stand for 24hr. at 37 ± 1^0.

Swelling capacity was expressed as percentage and calculated using following formula

$$\text{Swelling Capacity} = (xv/xi) \times 100$$

Xv = Final volume occupied by swollen material after 24hr.
Xi = Initial volume occupied by powder in measuring cylinder.

$$\text{Swelling Index (SI)} = \frac{\text{Final volume} - \text{Initial volume}}{\text{Initial volume}} \times 100$$

The swollen mass from measuring cylinder, at the end of test period was removed and weighed (gram) to get the final weight and percentage increase in weight was determined by use of following equation

$$\text{Increase in weight (\%)} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percentage increase in weight was interpreted for water uptake capacity of the test polysaccharides. The reduction in SI of modified polysaccharides in comparison to pure Polysaccharide was determined by the following equation [6].

$$\text{Reduction in SI} = \frac{\text{SI of polysaccharide} - \text{SI of modified polysaccharide}}{\text{SI of polysaccharide}}$$

Hydration capacity (H.C.)
Disintegrant (1gm) was taken in the 15ml tarred centrifuge tube. Then 10ml of distilled water was added to it and allowed to centrifuge for 10min. after the centrifugation process the tarred centrifuge tube was taken out and inverted to remove the supernent. The decanted tube then weighed on digital balance and the hydration capacity was calculated using following equation.

$$\text{H.C.} = \frac{\text{Weight of hydrate sample}}{\text{Weight of dry sample}}$$

Density
The loose bulk density (LBD) and tapped bulk density (TBD) of disintegrants were determined. Disintegrant (2g) was poured in to calibrated measuring cylinder (10ml) and noted initial volume. Then the cylinder was allowed to fall under its own wight onto the hard surface from the height of 2.5 cm at 2 second intervals. The tapping was the continued until no further change in volume was noted. LBD and TBD wew calculated using following equations,

LBD = weight of the powder/ volume of the packing

TBD = weight of the powder / tapped volume of the packing

Compressibility
The compressibility index (Carr's index) was determined by using following equation,

Carr's index % = [(TBD-LBD) X 100] / TBD

Preparation of Orally disintegrating Tablets
Orally disintegrating tablets of Fexofenadine HCL was prepared by direct compression method. The drug and excipients were passed through sieve (#80) to ensure better mixing. Microcrystalline cellulose and Mannitol as a direct compressible vehicle. Superdisintegrants

Crosspovidone, agar, treated agar and, co- grinded modified polysaccharide were used in different proportions (5 and 10%) as shown in **Table 1.** The powders were compressed using a rotary 10 station tableting machine (Ratanakar Machinery Co. Pvt. Ltd., India) equipped with round, flat and plain punches [7]

Table 1: The composition of Orally Disintegrating tablets FXD HCL

Ingredient (mg)	FORMULATIONS CODE							
	Fdt1	**Fdt2**	**Fdt3**	**Fdt4**	**Fdt5**	**Fdt6**	**Fdt7**	**Fdt8**
Fexofenadine HCL	30	30	30	30	30	30	30	30
AG	15	30	-	-	-	-	-	-
TAG	-	-	15	30	-	-	-	-
C-TAG	-	-	-	-	15	30	-	-
Cross-povidone	-	-	-	-	-	-	15	30
MCC (Avicel PH-102)	100	100	100	100	100	100	100	100
Mannitol (Pearlitol SD200)	137	122	137	122	137	122	137	122
Sodium Saccharine	6	6	6	6	6	6	6	6
Mg stearate	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6
Total	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**

***** *Quantity expressed in mg/tablet where AG represents AGAR, TAG represents treated AGAR, and C-TAG represents co-grinding treated AGAR*

Evaluation of Fast Dissolving Tablets
Quality control tests for ODTs of all formulations were performed, and the average values were calculated [8].

Drug-excipients interaction studies
The pure drug sample, agar, treated agar and modified treated agar and physical mixture of drug to excipients were subjected to I.R. spectral studies using FTIR spectrophotometer (FTIR Alpha Model, Brukar, Japan)

Sensory Evaluation
The prepared tablets were sensory evaluated for the color, odor taste and for roughness and irritation. For taste, roughness and irritation, six healthy volunteers were selected. They were asked to keep the tablet in the mouth without biting and without drinking water. Immediately

after the sensory evaluation, volunteers were asked to rinse the mouth without ingesting disintegrating particles6.

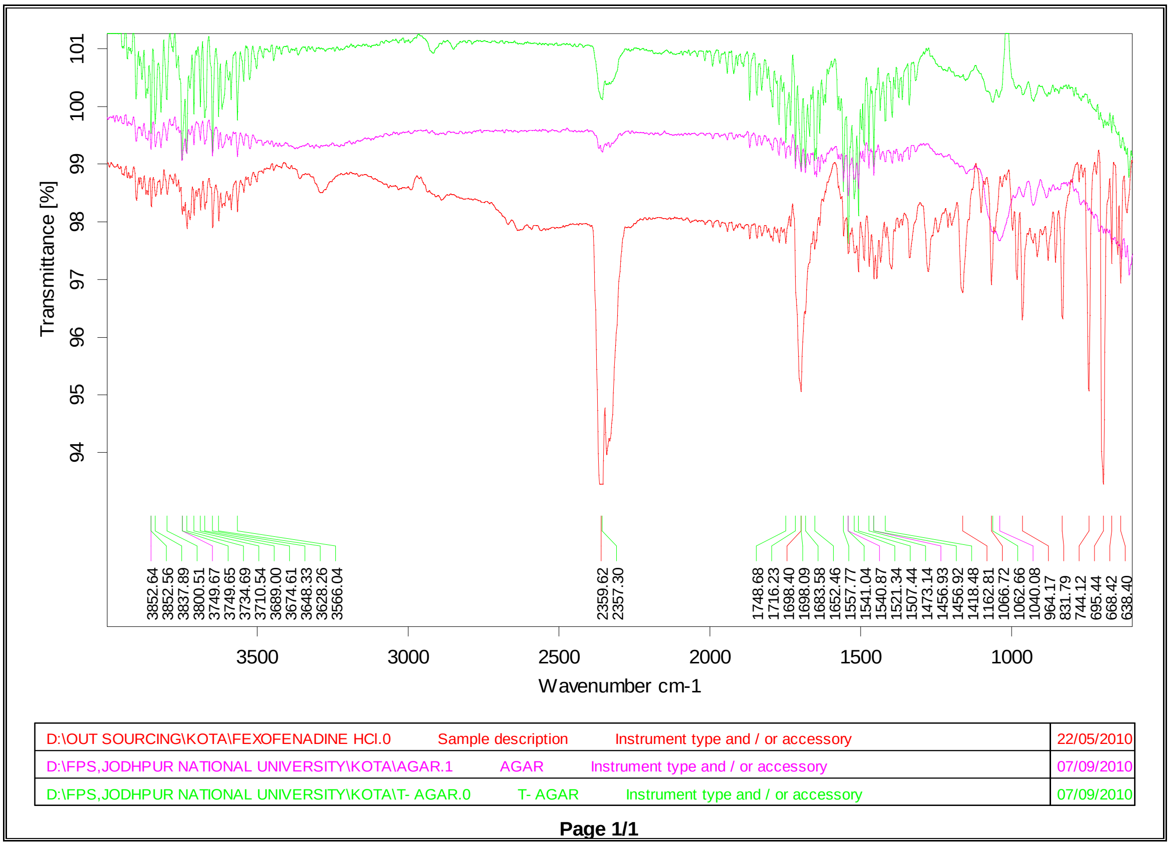


Fig: 2. FTIR Spectra of drug, AG, TAG

Thickness and Diameter

The thickness and diameter of the prepared tablets were measured using Digital Vernier Caliper. It is expressed in mm.

Weight Variation

Weight variation was determined by weighing 20 tablets individually; the average weight and percent variation of tablet was calculated individually.

Hardness and Crushing Strength

Hardness was determined by taking ten tablets from each formulation, using a Monsanto tablet hardness tester and the average of applied pressure (kg/cm2) for crushing the tablet was determined.

Friability

The friability of the tablet was determined by electrolabe Friabilator. Initially weighed (Wo) 20 tablets after dusting and placing them in a friability tester, which was rotated for 4 min at 25 rpm. After dusting, the total remaining mass of tablets (Wf) was recorded and the percent friability was calculated by

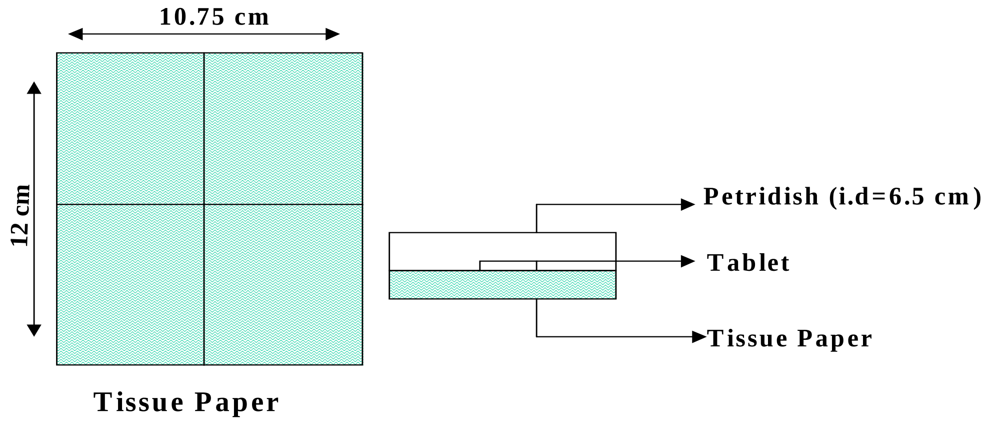
$$\% \text{ Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

Drug content

Twenty tablets were weighed and powdered. An amount of the powder equivalent to 30mg of Fexofenadine HCL was dissolved in 100ml of pH 6.8 phosphate buffer, filtered, diluted suitably and estimated for the drug content at 259nm using UV-Visible spectrophotometer (UV 1800-Shimadzu, Japan).

Wetting time

A piece of tissue paper (12cmx10.75cm) folded twice was placed in a Petri dish containing 6ml of water. A tablet was placed on the paper and the time taken for complete wetting of tablet was noted 9. Three tablets from each formulation were randomly selected and the average wetting time was noted.



Simple Method for the Measurement of Wetting Time of a Tablet

Uniformity of dispersion

Three tablets were randomly selected and dispersed in 100ml of water. The resulting dispersion was passed through sieve No.22.

***In- vitro* disintegration time**

In vitro disintegration time was measured by placing a tablet in 100ml water maintained at 25°C. The time taken for the tablet to disintegrate completely was noted [10].

Dissolution studies

In- vitro drug release studies of all the formulations were carried out using tablet dissolution test apparatus (USP TDT 06 PL, Electro lab, Mumbai) at 50rpm. Phosphate buffer pH6.8 was used as the dissolution media with temperature maintained at 37±1°C. Samples were withdrawn at different time intervals, diluted suitably and analyzed at 259nm for cumulative drug release using Shimadzu UV-Visible spectrophotometer. The sample after each withdrawal was replaced with same volume of fresh media and the test was conducted in triplicate [11].

RESULTS AND DISCUSSION

Particle size distribution of AG, TAG and Co- grinded TAG were found different .Particles retained over sieve # 100 were 13.6%, 63.8% and 64.4% for AG, TAG and Co-grind TAG respectively. **(Table 2**)

Table 2: Particle Size Distribution of AG, TAG and C-TAG

Size (mesh)	Agar	TAG	Co-grind Treated Agar
	Weight (%)		
20/40	0	8.6	8.4
40/60	1.6	24.45	25.13
60/100	19.5	34.13	31.4
100pass	86.4	36.2	35.6

Water treatment produced coarse particles in AG and TAG. Particle size is one of the factors that affect disintegration activity. A larger particle size and hence increased porosity leads to a faster wicking and swelling of disintegrants. Larger particle size probably yielded greater pore size and altered the shape of the pore. Coarse particles of AG, TAG and co- grinded TAG were confirmed by SEM image shown in F**ig 1**.

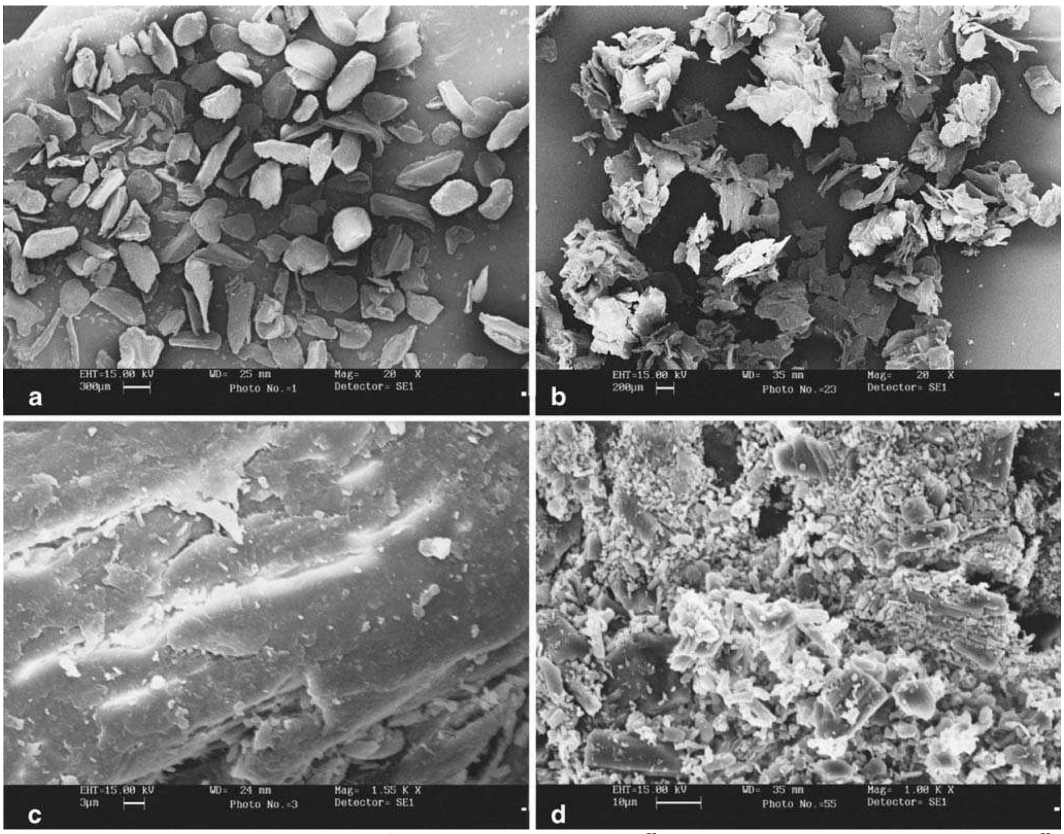


Fig. 1. Scanning electron micrographs of a AG, (original magnification ×20); b TAG, (original agnification ×20); c surface morphology of TAG, (original magnification ×500); d C-TAG, (original magnification ×20)

Larger particles of disintegrants swelled more rapidly and to a greater extent than the smaller particles. So C-TAG and TAG has taken less time for disintegration of the tablet than AG containing tablet.

Powder properties like compressibility index, angle of repose, loss on drying, LBD, TBD, and moisture absorption capacity represented in **Table 3.**

LBD of C-TAG was found to be less than TAG and LBD of TAG were found to be less than AG (C-TAG 0.321g/ml, TAG 0.341g/ml and AG 0.393.g/ml) indicates more porous structure of –C-TAG and TAG than AG. Therefore, tablets prepared from C-TAG AND TAG had faster wicking and swelling hence faster disintegration than AG containing tablets.

Table 3: Powder Properties of AG, TAG and C-TAG

Disintegrants	Angle of repose	LBD (g/ml)	TBD (g/ml)	Compressibility Index (%)	Hausner's Ratio
AG	28.23	0.393	0.481	18.23	1.22
TAG	13.48	0.341	0.412	17.27	1.20
C-TAG	10.78	0.321	0.371	13.45	1.15

Swelling and hydration capacity of disintegrants are the important parameters for comparing disintegration efficiency represented in **Table.4.** Higher swelling and hydration capacity of Crosspovidone leads to faster disintegration of batch ODT7 and ODT8.Higher swelling and hydration capacity C-TAG leads to faster disintegration than TAG and AG.

Table 4: Disintegrants Powder Properties

Disintegrants	Swelling capacity (%)	Hydration capacity (g water/g polymer)
Cross-povidone	516.92	9.14
Agar	405.38	6.23
TAG	445.62	7.56
C-TAG	482.61	8.69

Table 5: Tablets Properties

Batch	Weight (mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Wetting Time (sec.)	In-vitro Disintegrating Time (sec.)
Fdt1	Pass	3.9	0.36	99.2	75	81
Fdt2	Pass	3.8	0.23	99.5	62	68
Fdt3	Pass	3.6	0.34	99.4	64	67
Fdt4	Pass	3.4	0.34	99.8	58	63
Fdt5	Pass	3.5	0.56	98.2	56	59
Fdt6	Pass	3.6	0.43	99.6	50	55
Fdt7	Pass	3.3	0.53	99.4	45	43
Fdt8	Pass	3.5	0.36	99.7	40	47

Disintegration and dissolution test of all batches were performed by using distilled water showed that cross-povidone was found to be best among all disintegrants used. C-TAG containing tablets found to disintegrate faster than tablets containing TAG and AG. Disintegration time and Wetting time for all batches shown in Table.5

Cumulative percent drug release verses time plot of all batches shown in F**ig.5**

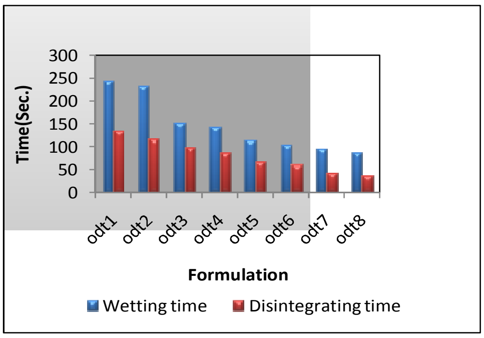


Fig.3: Effect of various disintegrants on disintegration time and wetting time

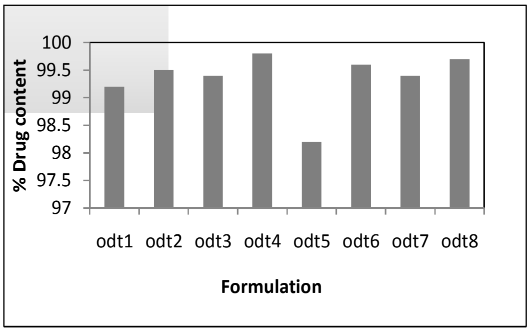


Fig.4: % of drug content in different formulation

Faster wetting occur for tablets in batch ODT7 and ODT8 containing cross-povidone due to capillary action. Wetting time of tablets was found in decreasing order as cross-povidone < C-TAG <TAG < AG. The advantages of the C-TAG and TAG over existing superdisintegrants are cheap, easily available with simple processing and specifically cut down the cost of final formulation.

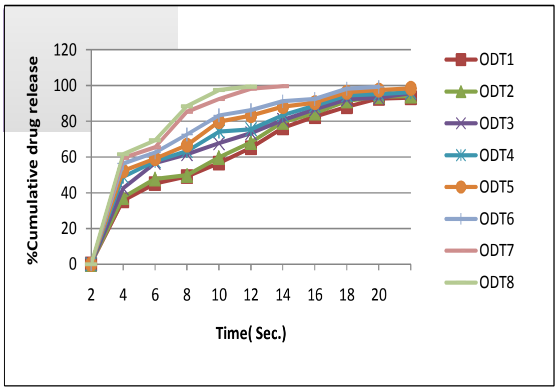


Fig 5: in vitro % cumulative drug release

CONCLUSION

AG was reported as disintegrants but it is less effective. Disintegration efficiency of AG was increased by water treatment. TAG was found to be more effective than AG. Among all the disintegrants used, cross-povidone was found to be more effective due to its high swelling capacity. TAG is more effective than AG and also quite comparable with existing superdisintegrants. As TAG is cheap, easily available with simple processing it can use as an alternative to many disintegrants like agar. Also further modifications in agar should not be ignored as it can produce a disintegrants superior than used superdisintegrants.

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