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PHARMACEUTICAL EVALUATION OF DIFFERENT SUPER DISINTEGRANTS IN DESIGN OF METOPROLOL TARTRATE ORODISPERSIBLE TABLETS

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ABSTRACT

Purpose: The Purpose of the present study was to develop orodispersible tablets of metoprololtartrate (beta blocker used in treatment of angina pectoris, hypertensionand congestive heart failure.) for improving patient compliance, especially, those of paediatric and geriatric categories facing problem or difficulties in swallowing. Orodispersible tablets of metoprololtartrate Prepared with different super disintegrates by using direct compression method. **Methods:** Orally disintegrating tablets of metoprololtartrate was prepared using three different super disintegrates namely croscaramellose sodium, crospovidone and sodium starch glycolate with three concentrations (3%, 6% and 9%) were prepared by direct compression method. The final blend of the drug and excipients were evaluated for powder flow properties, bulk density, tapped density and compressibility index. All the formulations were evaluated for weight variation, thickness, disintegration time, hardness, friability, wetting time and water absorption ratio. **Results**: The optimised formulation F4 containing 3% w/w crospovidone, showing maximum drug release within 10min. Short-term stability studies (at 40±2o/75±5% relative humidity) on the best formulation indicated that there are no significant changes in drug content and in vitro disintegration time. FTIR-spectroscopic studies indicated that there are no drug–excipients interactions. **Conclusions**: The present study clearly demonstrates that orodispersible tablets of metoprololtartrate could be

successfully prepared by direct compression method and It can be concluded that the tablets containing 3% crospovidone F4 formulation is optimized due to its fast in-vitro dispersion when compare to other formulation.

Keywords: Metoprololtartrate, orodispersible tablets, super disintegrant, crospovidone, croscaramellose, sodium starch glycolate.

INTRODUCTION

Solid oral dosage forms like tablets and capsules are having wide acceptance about 50-60% of dosage forms and popularity because of ease of administration, accuracy in dosage, self-medication and patient compliance. Drawback of these dosage forms is difficulty in swallowing with water. Often times patients experience inconvenience due to motion sickness (kinetosis), sudden episodes of coughing and unavailability of water allergic condition and bronchitis. Hence, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great attention. To fulfil these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as orally disintegrating tablets (ODTs) which disintegrate very rapidly (sec) in saliva without the need of water. Drug dissolution, absorption, drug bioavailability and clinical effect were observed to be significantly greater than conventional dosage form. Recently ODT terminology has been approved by United States Pharmacopoeia, British Pharmacopoeia and Centre for Drug Evaluation and Research (CDER)[1].

Metoprololtartarate is a cardio selective beta-1 adrenoreceptor blocker mostly used in the treatment of acute disorders such as angina pectoris and hypertension. It is a BCS (Biopharmaceutical Classification System) class-1 drug. It has high solubility and high permeability. Metoprololtartrate is freely soluble in water and methanol. The half life of Metoprololtartrate is approximately 3 to 4 hours. It undergoes extensive first pass hepatic metabolism resulting in 40% oral bioavailability.It is an ideal candidate for orodispersible drug delivery system. Hence the preparing orodispersibletablet of Metoprololtartarate lead to enhance the bioavailability and avoidance of first pass hepatic metabolism [2,4].Metoprololtartrate ODTs was prepared by direct compression method using three super disintegrates, croscarmellose sodium, crospovidon and sodium starch glycolateat different concentrations. The prepared tablets were evaluated and compared with three super disintegrates, effect on in vitro dispersion time, in vitro drug release and FTIR studies were observed. From nine formulations, the optimum formulations were selected[5].

MATERIALS AND METHODS

Materials

Metoprololtartrate was received as a gift sample from NatcoPharma, Pvt. Ltd, Hyderabad, India. Crospovidone, croscarmellose sodium, mannitol, aspartame, sodium starchglycolate, magnesium stearate, talc, microcrystalline cellulose, were purchased from S.D. Fine Chemicals Ltd., Mumbai, India.

Methods

Preformulation study for drug-excipient compatability

The spectrum analysis of pure drug, polymer and physical mixtures of drug and different excipients used for preparation of tablets was studied by FTIR. Spectra were recorded by preparing drug potassium bromide (KBr) discs using a Shimadzu Corporation (Koyto, Japan) facility (model - 8400S). The resultant disc was mounted in IR spectrophotometer and the spectrum was recorded from 4000 cm^{-1} to 500 cm^{-1} for 12 minutes [1].

All the ingredients were passed through mesh no 60. Required quantity of each ingredient was taken for each specified formulation[1]. The powder blend was evaluated for pre-compression parameters and shown in Table 2.

Preparation of orodispersible tablets of metoprololtartarate

Metoprololtartrateorodispersible tablets were prepared by direct compression method according to formula given in the table 1. Accurately weigh amount of drug to this super disintegrates (croscaramellose sodium, crospovidone and sodium starch glycolate at different concentrations 3%, 6% and 9%), and microcrystalline cellulose were mixed in small portion of both at each time and blended to get a uniform mixture and kept aside. Then the other ingredients were weighed and mixed in geometrical order passed through sieve no 20. Tablet were punched by using 8mm flat punch by rotary tablet compression machine, nine batches F1 to F9 were prepared with various proportion of super disintegrates and excipients. Before tablets preparation, the mixture blends of all the formulation were subjected for compatibility studies (FTIR) and pre-compression parameter like Angle of repose Bulk density, Tapped density and percentage compressibility [6].

Table 1:Formulation of metoprololtartrate tablets

Ingredients	Formulation code (Quantity in mg/tablet)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metoprololtartrate	25	25	25	25	25	25	25	25	25
croscaramellose sodium	6	12	18	-	-	-	-	-	-
Crospovidone	-	-	-	6	12	18	-	-	-
sodium starch glycolate	-	-	-	-	-	-	6	12	18
MCC	52	52	52	52	52	52	52	52	52
Mannitol	94	88	82	94	88	82	94	88	82
Aspartame	15	15	15	15	15	15	15	15	15
Aerosol	1	1	1	1	1	1	1	1	1
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	5	5	5	5	5	5	5	5	5

Evaluation Test

Precompression parameters of the blend

Precompression testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.

Angle of Repose

The frictional force in a loose powder can be measured by the angle of reposeθ. It is an indicative of the flow properties of the powder. It is defined as the maximum angle possible between the surface of pile of powder and the horizontal plane.

$$\theta = \tan^{-1}(h/r)$$

Where, θ-angle of repose,h-height of pile;r-radius of the base of pile

The powder mixture was allowed to flowthrough funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel.Volume of angle of repose less than 30°usually indicate a free flowing material and angle greater than 40°suggest a poorly flowing material[6].

Bulk density

Apparent bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume and weight of the powder was determined [5].It is determined by following equation,

ρb = W / Vb

Where, ρb = Bulk density, Vb = Bulk volume of blend (cm^3), M = Weight of power (gm).

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time (100 tapping). The minimum volume occupied in the cylinder and weight of the blend was measured[2]. It is determined by following equation,

ρt = W / Vt

Where, ρt = Tapped density**,** Vt = Final volume of blend after tapping (cm^3).

Carr's compressibility index: Carr's compressibility index is determined by following equation [2].

C = (ρt - ρb) /ρt × 100

Where, C = % compressibility, ρb = Bulk density, ρt = Tapped density.

Hausner's Ratio: This is an indirect index of ease of powder flow. [2]

It is calculated by following formula; **H = ρt /ρb**

Post compression parameters of the tablets

Thickness: The size of tablets was evaluated by Verniercallipers. (Table 3)[2]

Average Weight: Twenty tablets were selected at a random and average weight was calculated. Then individual tablets were weighed and the individual weight was compared with an average weight [7].

Hardness and Friability: Tablets were evaluated for hardness and friability test using Monsanto hardness tester and Roche friabilatorrespectively [7].

The percentage friability was then calculated by,

$$F = W_{initial} - W_{final} / W_{initial} \times 100$$

F= % Friability and W= weight

Content uniformity test: Four tablets weighted and crushed in a mortar then weighed powder contain equivalent to 10 mg of drug was taken and dissolved in 100 ml methanol, from this solution 1 ml of solution was diluted to 10 ml methanol again 1 ml solution from this diluted upto 10 ml with methanol and assayed for drug content at 275nm. [7]

Wetting Time and water absorption ratio:Wetting time and water absorptionratio is intimately related to thehydrophilicity of the excipient and to thepore size of tablets. A piece of tissue paperfolded twice was placed in a small Petri-dish(internal diameter of 6.5 cm) containing 10ml of water. A tablet was placed on thepaper and the time required for completewetting was measured. The wetted tabletwas then weighed.[7,8] Water absorption ratio'R' was determined using the equation,

R=(Wb-Wa)/ Wa x100

Where, Wa is weight of tablet before water absorption, Wb is weight of tablet after water absorption.

In-vitrodissolution Studies: Dissolution rate was studied by using USP type-II apparatus (USP XXIII Dissolution Test Apparatus at 50 rpm) using 900ml of phosphate buffer pH (7.4) as dissolution medium. Temperature of the dissolution medium was maintained at 37±0.5°C; aliquot of dissolution medium was withdrawn at every 5 min interval and filtered. The absorbance of filtered solution was measured by UV spectrophotometric method at 275 nm and concentration of the drug was determined from standard calibration curve [7,9].

In vitro dispersion time: This test is performed to ensure disintegration of tablets in the salivary fluid, if it is to be used as an orodispersible tablet. In vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing 6ml of simulated salivary fluid of pH 6.8. Three tablets from each formulation were randomly selected and in vitro dispersion time was measured [10].

RESULTS AND DISCUSSION

Preformulation study for drug excipient compatibility

FTIR spectrum study

FTIR spectra of the drug, excipients and optimized formulation were recorded in range of 4000-400cm^{-1}. In the optimized formulation F4 shows the presence of all the characteristics peaks of metoprololtartrate indicates no interaction between the drug and the excipients.The pure drug is not altered functionally as shown in the Fig 2.

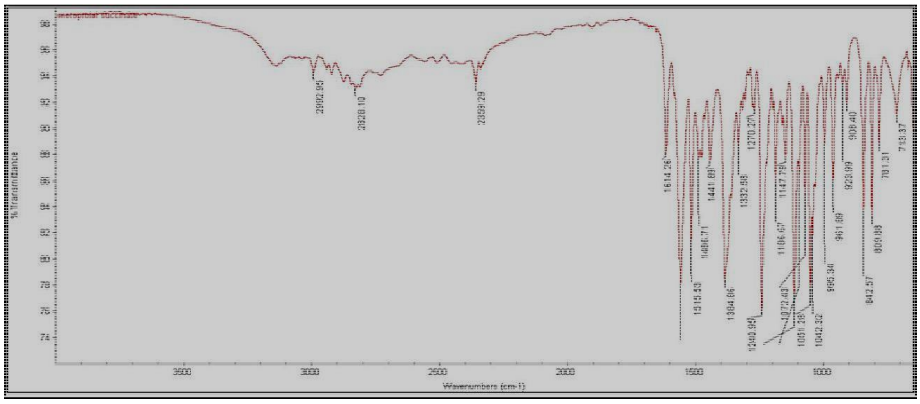

Fig. 1: Pure drug of metoprololtartarate FTIR spectrum

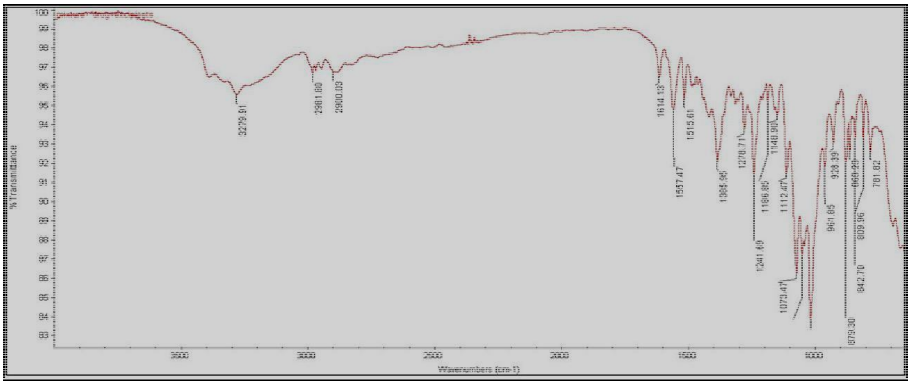

Fig. 2: Metoprololtartarate and excipients (crospovidone) FTIR spectrum.

Formulation

Nine formulations of Metoprololtartrate werepreparedby direct compression method with varyingconcentration of three super disintegratescroscarmellose sodium, crospovidone, sodium starchglycolate.Taste masking was done by flavours and sweeteners andmicrocrystalline cellulose was used as diluents.

Precompression evaluation test

Metoprololtartarate tablets and blend evaluated forvarious parameters as explained earlier. The powderblend was evaluated thephysical properties such as angleof repose, bulk density, tapped density, compressibilityindex and Hausner‘s ratio for the prepared tablet blendTable 2.

Angle of repose

The angle of repose between 31 and 35 indicates good free flowing material and >40° with poor flow properties. Values for angle of repose were found in the range of 30.9° to 32.9° showing that the blend of powder has good free flowing and can be used for direct compression.

Carr's index

The value for carr's index was in between 11.5 to 18.9 indicating that most batches of powder blends were having good or fair compressibility.

Hausner's ratio

Hausner's ratio was found to be within limits. All formulation blends showed good flow properties and hence tablets were prepared by direct compression method.

Table 2: Tablet blend evaluation test.

S.No	Formulation Code	Bulk Density	Tapped Density	Angle of Repose	Carr's compressibility index	Hausner Ratio
1	**F1**	0.45	0.63	30.9	18	1.20
2	**F2**	0.29	0.34	31.2	17	1.21
3	**F3**	0.24	0.29	31.4	18.9	1.23
4	**F4**	0.23	0.23	31.1	13	1.12
5	**F5**	0.35	0.41	29.8	13.8	1.15
6	**F6**	0.30	0.40	32.9	11.5	1.11
7	**F7**	0.24	0.29	31.2	16.7	1.21
8	**F8**	0.25	0.31	30.5	16.6	1.20
9	**F9**	0.38	0.44	30.8	17.5	1.19

Postcompression evaluation test

The postcompression parameters such as thickness, hardness, friability, weight variation, amount of drug content, in-vitro wetting time and in-vitro disintegration time were evaluated which are shown in table 3.

Thickness: The Thickness of all the tablets tested. For all the batches were found tobe within the pharmacopoeial limits. The Thickness of tablets of various batches was between 4.38-4.62 mm.

Average Weight: The weight variation of all the tablets tested. For all the batches were found tobe within the pharmacopoeial limits. The weights of tablets of various batches were between 197.9-202.1 mg.

Hardness and Friability: It is well known that the hardness of the tablet can markedly affect the release rate of drug. The hardness was found to be 2.3 kg/cm2. It indicates good mechanical strength with a capability to resist physical and perfunctory stress conditions during handling. The friability values of all the formulations are less than1% and they meet the pharmacopoeial Standards.

Table 3: Tablets evaluation test.

Formulation Code	Weight Variation (Mg)	Thickness (Mm)	Hardness (Kg/Cm2)	% Friability	Wetting Time(Seconds)	Content Uniformity(%)	Disintegration time (sec)
F1	200.5	4.48	2.3	0.67	53	95	73
F2	200.7	4.42	2.3	0.78	53	96	68
F3	201.1	4.62	2.3	0.70	44	94	50
F4	200.1	4.54	2.3	0.53	19	99	23
F5	197.9	4.38	2.3	0.62	23	98	44
F6	201.9	4.48	2.3	0.71	34	96	51
F7	198.2	4.61	2.3	0.59	70	97	125
F8	197.9	4.60	2.3	0.52	68	102	140
F9	202.1	4.59	2.3	0.72	71	103	181

Content uniformity test

The percentages drug contents of all the tablets were found to be ranging from94% to 103% which was within the acceptable limits mentioned in USP.

Wetting Time and water absorptionratio

The results of wetting time and water absorption ratio were found to bewithin the prescribe limits and satisfy thecriteria of orodispersible tablets. The wetting time and water absorption ratio of all the tablets were found to be between 19 to 71 seconds which was within the acceptable limits shown in table 3.

Invitro disintegration time

In-vitro dispersion test was done for all the formulation.Tablet disintegration was affected by the wicking andswelling of the disintegrates from the 9 formulations F4shown less disintegration time, 23 seconds whencompared with others super disintegrates. Crospovidone is used as a super disintegrates in F4 formulation.

In-vitro drug release

In-vitro drug release studies of prepared tablets F1 to F9using different super disintegrating agents by differentconcentrations. The maximum drug release for theformulation F4 containing crospovidone 3% is 96% within 10 min.The drug release of formulations F1, F2, F3 containigcroscaramellose sodium shows 87.8, 91.4, 84.9; F4, F5, F6 containing crospovidoneshows 96.3, 95.9, 93.0 and F7, F8, F9 containing sodium starch glycolateshows 73.9, 72.8, 73.7 respectively.

Table 4: In vitro drug release studies of croscaramellose sodium, crospovidone and sodium starch glycolate

Time(min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	50.8	51.3	55.3	62.4	59.5	59.2	45.6	44.6	45.6
5	58.7	75.5	67.2	76.6	71.3	72.1	54.5	56.8	52
7	75.8	87.8	78.3	88.8	86.6	83.8	66.6	65.7	65.5
10	87.8	91.4	84.9	96.3	95.9	93.0	73.9	72.8	73.7
15	94.9	95.1	96.4	95.8	95.1	94.3	82.2	85.8	82.9
30	96.2	91.7	95.3	94.4	93.2	96.1	93.8	94.1	92.4
45	92.8	90.1	94.7	92.8	92.8	92.6	92.7	93.2	93.5

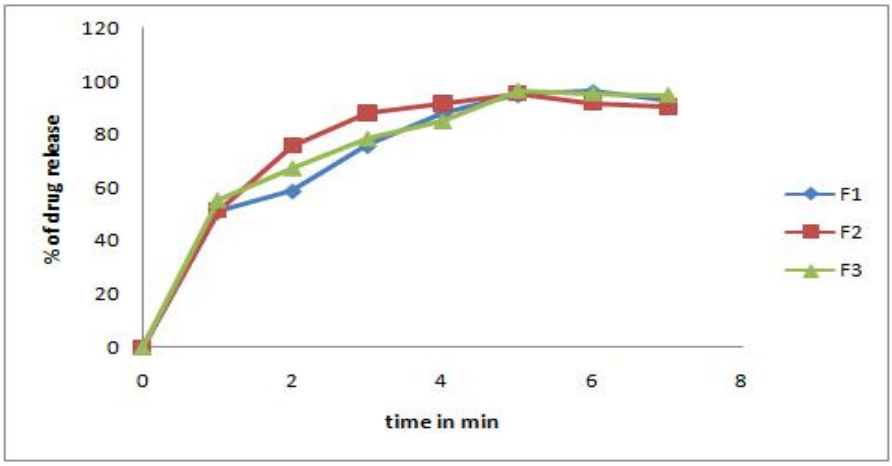

Fig. 3: In Vitro Drug Release Studies of Croscaramellose Sodium.

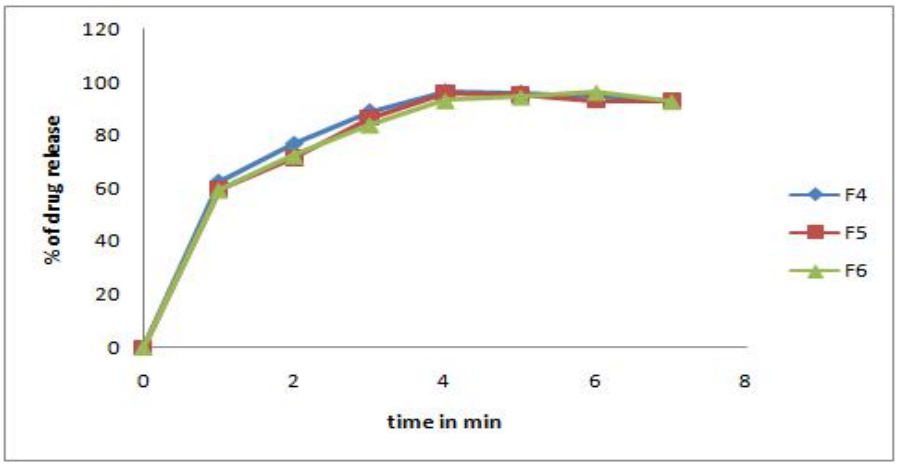

Fig. 4: In Vitro Drug Release Studies of Crospovidone

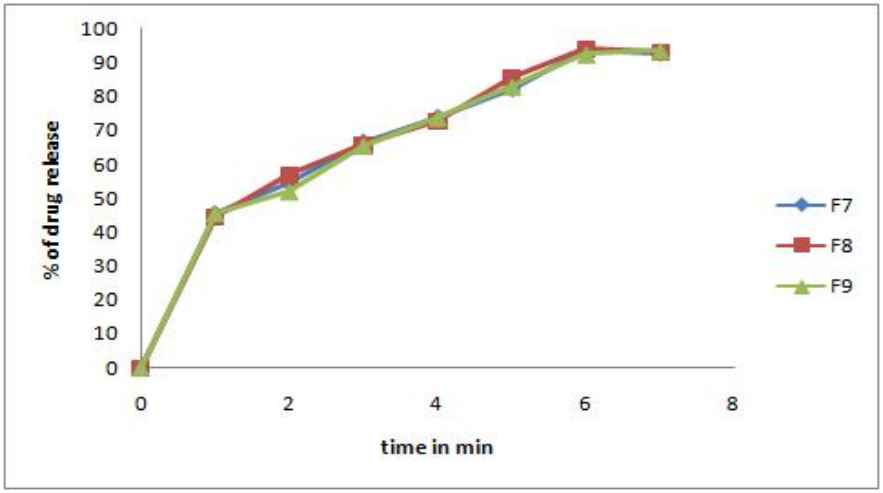

Fig. 5: In Vitro Drug Release Studies

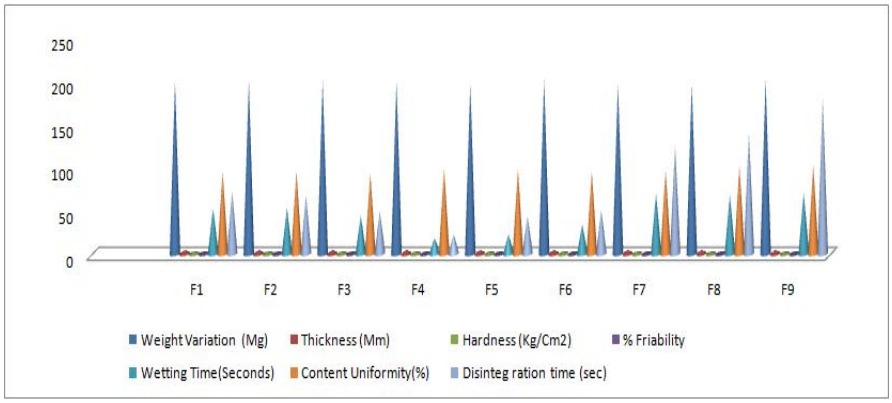

Fig. 6:Graph of All Evaluation Test Sodium Starch Glycolate

CONCLUSION

The FTIR studies show that there wasno interactionbetween the drug and the excipients. The formula was optimized for metoprololtartrateoro-dispersible tablets to give fast relief and to increase thepatient compliance. Batch F4 containing crospovidone 3% was found to be the best as compare to other formulations. F4 formulation is optimized due to its fast in-vitro dispersion, optimum hardness (2.3 kg/cm2), friability (0.53), wetting time (19 sec.) and disintegration time of (23 sec). The conclusive finding in this study is that orodispersion was better with formulation containing crospovidone than those with croscaramellose, sodium starch glycolate and on an observatory note it can be hypothesized that mannitol might be acting as a hindering agent in orodispersion process.

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