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OPTIMIZATION AND EVALUATION OF TELMISARTAN FAST DISSOLVING TABLETS EMPLOYING STARCH GLUTARATE -A NEW SUPERDISINTEGRANT.

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ABSTRACT

Telmisartan is a Anti-hypertensive drugs which is insoluble in water, hence the drug may be slowly or incompletely dissolves in the gastro-intestinal tract. So the rate of dissolution and therefore its bioavailability is less (bioavailability 42%). The dissolution rate of telmisartan can be increased by formulating it into fast dissolving tablets, as these dosage forms disintegrate very rapidly into fine suspension of drug particles resulting in higher surface area of drug. Though, several disintegrants are available, there is continuous need to develop newer disintegrants to have more disintegration and dissolution efficiency. The present research work involves preparation, characterization and evaluation of starch glutarate as a super disintegrant. The prepared starch glutarate was found to be free flowing and FT-IR revealed the formation of ester. In the present research work, 2^3 factorial design was used for optimization of level of independent variables (starch glutarate, sodium starch glycolate and croscarmellose sodium) on dependent variables (disintegration time and percent released in 10 minutes) in the formulation Telmisartan fast dissolving tablets with less experimentation. From the results it was concluded that starch glutarate, (5%), sodium starch glycolate (5%) and croscarmellose sodium (5%) were favourable for formulation of Telmisartan fast dissolving tablets. Therefore, starch glutarate a new modified starch was found to be a promising disintegrant in the formulation of fast dissolving tablets of poorly soluble drugs.

KEYWORDS: Poorly Soluble, Telmisartan, Starch glutarate.

INTRODUCTION

Telmisartan is a nonpeptide angiotensin receptor II (Type- ATI) antagonist, that cause inhibition of the action of angiotensin II on Vascular Smooth Muscle in the symptomatic treatment of Hypertension. The bioavailability of Telmisartan is poor about 45%, which due to extensive first pass hepatic metabolism. The bioavailability can be increased by fast dissolving formulations.

MATERIALS AND METHODS

Telmisartan was gift from yarrow chemical Pvt. Ltd Mumbai. croscarmellose sodium and sodium starch glycolate, microcrystalline cellulose were supplied from crescent Chemicals Pvt. Ltd. Hyderabad. glutaric acid and potato starch obtained from yarrow chemical Pvt. Ltd. Magnesium stearate was supplied from loba chemi Pvt. Ltd., Mumbai. Buffer and its dilutions were prepared with double-distilled water.

METHODS

Preparation of Starch glutarate (a novel disintegrant)

Initially starch slurry was prepared. To the slurry glutaric acid was added and conditioned for 45 minutes. After conditioning, pH was maintained at 3.0 by addition of 10M sodium hydroxide. The precipitated starch glutarate was filtered, dried and passed through sieve no 100 to form fine powder.

Characterization of starch glutarate.

Starch glutarate was characterized by DSC and FTIR studies. Physical properties such as solubility, bulk density, tapped density, angle of repose and carrs index were also performed.

Preparation of Telmisartan Fast dissolving Tablets Employing Starch glutarate as Super Disintegrant

Tablets containing 50mg of Telmisartan were prepared by direct compression method employing starch glutarate as a super disintegrant in the concentration of (5-10%). Similarly Telmisartan fast dissolving tablets employing sodium starch glycolate and crosscarmellose sodium were formulated and compared with the formulations containing starch glutarate.

Table 1: Formula of Telmisartan Fast Dissolving Tablets Employing Starchglutarate.

Ingredient(Mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8
Telmisartan	40	40	40	40	40	40	40	40
starchglutarate	---	10	---	10	---	10	---	10
SSG	---	---	10	10	---	---	10	10
CCS	---	---	---	---	10	10	10	10
Mannitol	30	30	30	30	30	30	30	30
MCC	112	112	112	102	112	102	102	92
Talc	4	4	4	4	4	4	4	4
Magnesium Stearate	4	4	4	4	4	4	4	4
Total weight	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of pure drug, starchglutarate were recorded on samples prepared in KBr (2 mg sample in 200 mg KBr). The scanning range was 400 to 4000 cm−1 using FTIR Spectrophotometer.

Differential Scanning Calorimetry (DSC)

The DSC thermograms were recorded on a DSC (model 50, Shimadzu). Samples of 2 mg weight were heated in hermetically sealed aluminum pans over a temperature range of 30˚C to 300˚C at a constant rate of 10˚C/min under nitrogen purge (40 ml/min).

X-ray Diffraction (XRD)

XRD patterns were obtained using a CuKα monochromated radiation. Diffractograms were run at a scanning speed of 8˚/min over a 2θ range of 0˚ to 80˚.

Evaluation of Telmisartan Fast dissolving Tablets.

Tablets were evaluated for hardness, flexibility, weight variation, thickness, and disintegration time[2]. Hardness and friability were determined by Monsanto hardness tester and friability by Roche fibrilator. Weight variation was determined by using an electronic balance. Thickness of tablet was determined by vernier-calipers.

***In-vitro* Dissolution Studies**

In-vitro dissolution of Telmisartan was performed by according to USPXXIII type II dissolution apparatus in 900ml of pH 1.2 at 37±0.5^{0}C at 75 rpm. The samples were withdrawn at various time intervals and analysed spectrophotometrically at 212 nm.

Validation of optimized formulations

A check point analysis was performed to confirm the role of the derived polynomial equation in predicting the responses. Three check print formulations were prepared and evaluated to validate the design.

RESULTS AND DISCUSSION

Table 2: Physical and micromeritics properties of the starchglutarate.

Parameters	Observation
Solubility	Insoluble in all aqueous and organic solvent tests
pH(1%w/v aqueous dispersion)	3.72
Melting point	Charged at 300 Cº
Viscosity(1%w/v aqueous dispersion)	1.04cps
Swelling index	66.6%
Gelling properties	No gelling and the swollen particles of starchglutarate separate from water. where as in the case of starch, it was gelatinized and formed gel.
Moisture absorption	4.1
Partial size	152µm (80/120) mesh
Density	0.514g/cc
Bluk density	0.562g/cc
Angle of response	13.03Cº
Compressibility	15.53%

Characteristic of starchglutarate

Prepared starch glutarate was found to be fine, white coloured, odourless and slight acidic taste in nature. Starch glutarate was found to be practically insoluble in aqueous media (distilled water, pH 1.2, 4.5 and 7.4 buffers) and organic solvents (acetone, alcohol and chloroform). The results of micromeritic studies indicated free flowing character of starch glutarate.

Flow Properties: The flow properties of starchglutarate powder were analysed before compression to fast dissolving tablets By using bulk density, tap density, hausners ratio and Carr's index. The hausners ratio below 1.25 shows good flowability for direct compressible tablet. The Carr's index is between 12 to 21 shows good to fair flowability. The angle of repose between 31 to 40 shows good to fair flowability of powder.

Fourier Transform Infrared Spectroscopy

The FTIR studies were performed to check the possible interaction of the drug with the polymer. IR spectra of pure Telmisartan, Starchglutarate and their formulations are shown in fig. 3 shows the FTIR of Telmisartan, starchglutarate, The spectrum of pure Telmisartan

depict the characteristic peaks at 3058.74 cm-1 (aromatic C-H stretch), 2958.92 cm-1 (aliphatic C-H stretch), 1696.72 cm-1 (COOH acid), 1599.53 cm-1 (aromatic C=C bend and stretch), 1461.11 cm-1 (C-H bend), 1383cm-1 (OH bending and C=O stretching of COOH acid), 742.30 cm-1 756.85 cm-1 (ring vibration due to 1,2 disubstituted benzene), respectively.

The presence or absence s of characteristic peaks associated with specific structural group of the drug molecules was noted. The chemical interaction has been reflected by changes in the characteristic peaks of TEL, depending on the degree of interaction. The FT-IR spectra showed shift in peaks and also absence of peaks of Starchglutarate and TEL indicating chemical interaction between starchglutarate and TEL during fusion. The FTIR spectra showed the absence of the characteristic peak of TEL at 3058 cm-1 (aromatic C-H stretch) and shifting of 2958.92 cm-1 (aliphatic C-H stretch), 1461.11 cm-1 (C-H bend), 1383.43 cm-1 (OH bending and C=O stretching of – COOH acid). There were no extra peaks observed in the IR spectrum of solid dispersion. This established that the drug Telmisartan and starchglutarate used in the study showed no interaction and indicated that they were compatible with each other.

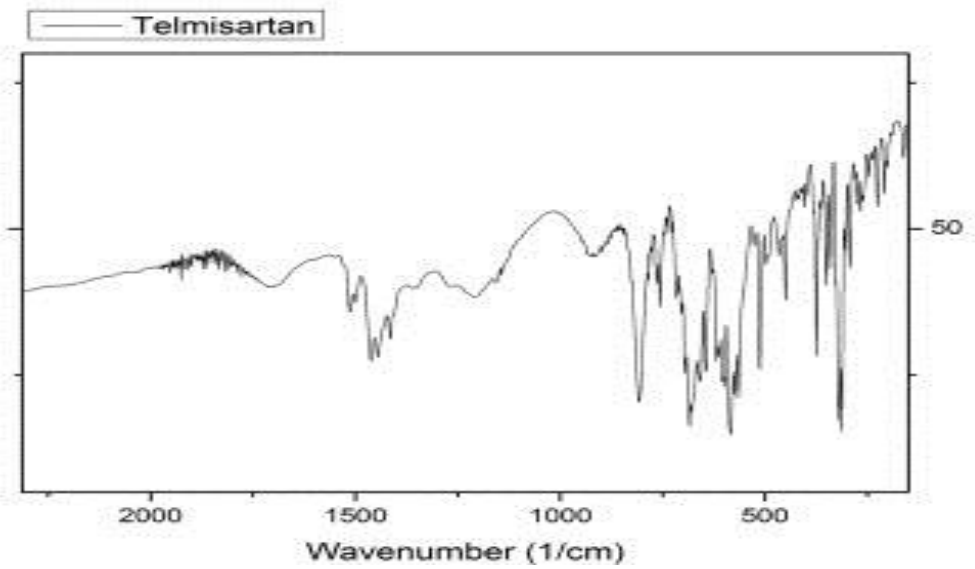


Figure 1: FTIR spectra of Telmisartan.

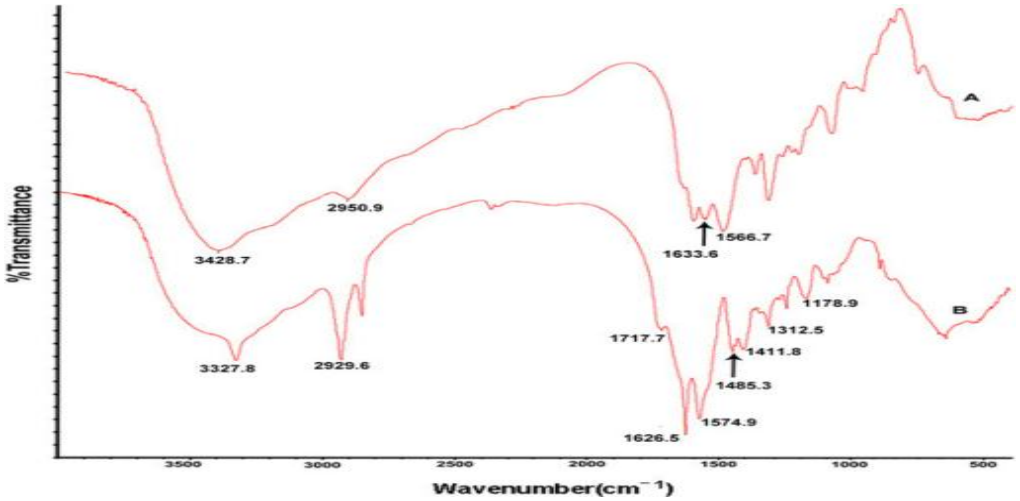


Figure 2: FTIR spectra of pure drug and starchglutarate.

DSC analysis

The DSC runs for Telmisartan, Starchglutarate and solid dispersion (prepaerd by fusion method) are shown in fig. 3. The DSC curve of pure TEL and SG exhibited single endothermic peaks at 268.46^{O}C (TEL) and 59.35^{O}C (SG) which corresponded to their intrensic melting points. The characteristic peaks of star werechglutarate invariably identified in the DSC curves of SD, suggesting that the starchglutarate was present in the same physical state after making the SD powder by the fusion method. No charateristic melting peak of TEL was identified in the DSC curves obtained from these starchgularate based SD formulation. This might be due to the higher polymer concentration and uniform distribution of drug in the crust of polymer, resulting in complete miscibility of molten drug in polymer. Absence of peak for the drug indicates that the drug is distributed homogenously in an amorphous state within in the solid dispersions without any interaction.

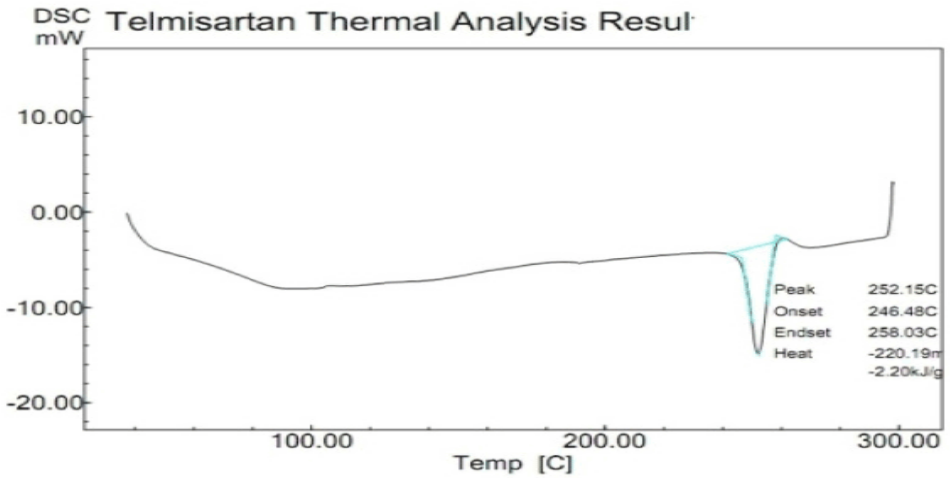


Figure 3: DSC studies of telmisaratn.

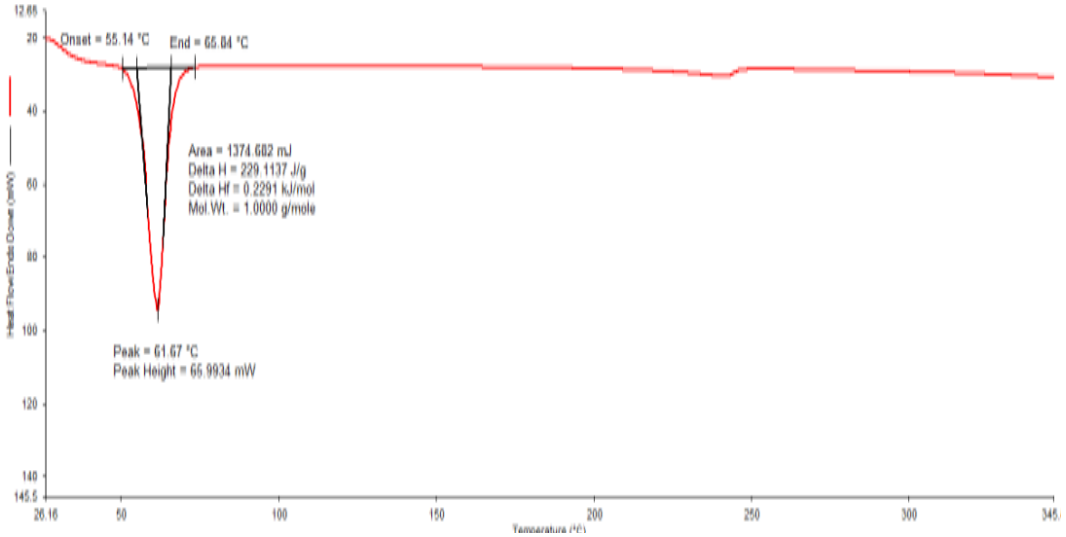
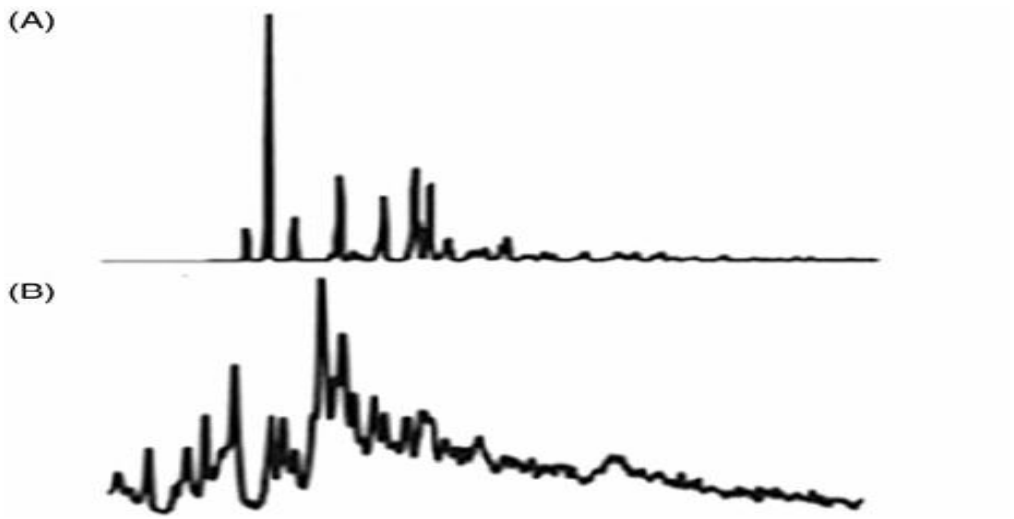


Figure 4: DSC studies of telmisaratn and starchglutarate.

XRD Analysis

XRD pattern of pure Telmisartan, starchglutarate and solid dispersion are shown in fig. 5. The XRD pattern of Starchglutarate had two characteristic peaks of high intensity at 19.0^{O} and 23.0^{O}. In the X-ray diffractrogram of Telmisartan, sharp peaks at diffraction angle (2θ) were 6.0^{O}, 14.0^{O}, 18.0^{O}, 23.0^{O}, 25.0^{O} indicate the presence of highly crystalline in nature and the main peak at 6.0^{O} was particularly more distinctive. It is known that the lack of a distinctive peak of a drug in SD systems demonstrates that a high concentration of the drug is dissolved in the solid state.



XRD studies of telmisartan and starchglutarate

Table 3: physical properties telmisartan fast dissolving tablets.

formulation	Hardness Kg/cm2	Friability (%)±S.D	Drug content (mg/tab)±S.D	Disintegration Time(s)±S.D	Wetting time(sec)±S.D	Water Absorption (%)±S.D
F1	3.9±0.003	0.12±0.032	38.21±.0.11	4±04	250±0.11	128.5±0.01
F2	4.0±0.002	0.13±0.053	39.32±0.57	1±05	115±1.34	95±0.04
F3	3.8±0.006	0.14±0.057	34.81±0.17	1±02	87±1.8	55±0.05
F4	3.6±0.023	0.11±0.078	37.52±0.54	1±09	72±0.56	95±0.09
F5	3.9±0.037	0.12±0.024	39.51±0.55	1±06	51±0.15	131±0.31
F6	3.8±0.034	0.15±0.059	38.42±0.64	1±04	90±0.37	147±0.52
F7	3.7±0.046	0.12±0.078	39.92±0.78	1±08	32±1.23	123±0.44
F8	3.9±0.043	0.14±0.095	28.21±0.11	1±07	77±0.45	160±0.21

Table 4: Dissolution data of telmisartan fast dissolving tablets employing.

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
5	4.7	29.7	29.7	31.5	19.7	56.1	45.6	92.8
10	8.1	37.8	37.2	44.4	24.2	76.6	53.3	100.9
15	20.2	68.3	61.7	65.3	54.7	85	68.7	
20	37.6	97.8	92.5	79.8	63.4	91.1	83.3	
30	45.9			90.6	80.9		95	

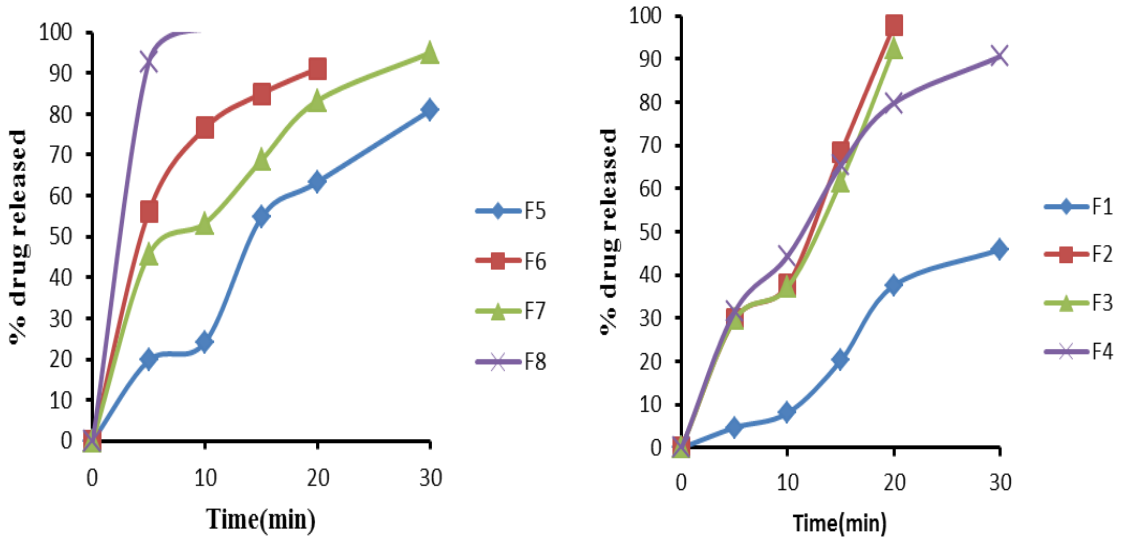


Figure 5: comparative different dissolution profiles of telmisartan fast dissolving tablets.

Table 4: Dissolution parameter of telmisartan fast dissolving tablets employing.

Parameters	F1	F2	F3	F4	F5	F6	F7	F8
PDs	5.67	96.87	77.56	97.89	85.98	99.67	96.56	99.80
DEs(%)	4.5	81.04	63.2	80	76.5	94.4	88.6	94.05
Increase in DEs no of folds	---	0.055	0.071	0.058	0.058	0.047	0.050	0.074
$K_1(min^{-1})$	0.253	0.695	0.195	0.396	0.369	---	0.677	---
Increase in $K_1(min^{-1})$ no of folds	----	0.364	0.327	0.638	0.638	---	0.373	---
Disintegration time (sec)	4	1	1	1	1	1	1	1

The results indicated that the hardness, friability, weight variation and thickness were within the IP limits. The polynomial equations are derived based on the results disintegration time and percent released in 10minutes to know the main and interaction effects of independent variables (starch glutarate, sodium starch glycolate and crosscarmellose sodium,) on dependent variables (disintegration time and percent release in 10 minutes) of the Telmisartan fast dissolving tablets.

The release rate Telmisartan from fast dissolving tablets was determined using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl 4) at 37 C and 75 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at 5, 10, 20, 30,45 and 60 min. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through a 0.45 µm membrane filter. Absorbance of these solutions was measured at 212 nm using a elico SL 21dobule UV/Vis spectrophotometer.

Cumulative percentage of drug release was calculated given in table no 5 using an equation obtained from a standard curve.

CONCLUSION

Starch glutarate prepared by reacting potato starch with glutaric acid was amorphous and non hygroscopic. All the fast dissolving tablets of Telmisartan prepared by employing starch glutarate as disintegrant gave rapid dissolution of Telmisartan fulfilling the official standards. 2^3 design was useful in predicting the optimum concentrations of sodium starch glutarate (A), sodium starch glycolate (B) and croscaramellose sodium (C) on disintegration time and percent released in 10 minutes within less experimentation in less time. From the results we can conclude that 5% croscarmellose sodium, 5% sodium starch glycolate and 10% starch glutarate were favourable for formulation of fast dissolving tablets with less disintegration

time and more percent released in 10 minutes which are the crucial factors in the formulation of the fast dissolving tablets.

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