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COMPARATIVE STUDY ON EFFECT OF NATURAL AND SYNTHETIC SUPERDISINTEGRANT ON FORMULATION OF SUBLINGUAL TABLET OF AMLODIPINE BESYLATE

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ABSTRACT

Amlodipine besylate which is generally taken to reduce hypertension. In this study an attempt has been made to formulate a dosage form of amlodipine using synthetic superdisintegrant crosscarmellose sodium to show that this synthetic superdisintegrant will show better disintegrating property than the natural superdisintegrant like sodium guar gum in the formulation of sublingual tablet of amlodipine besylate. Sublingual tablet prepared by direct compression technique using natural & synthetic superdisintegrant in different concentration & evaluated. Among all F6 is an optimized formulation of crosscarmellose sodium that releases the drug above 90% within 60 min. as compared to all formulations of natural superdisintegrant which is a guar gum preparation.

KEYWORDS: Amlodipine besylate, sublingual tablets, Superdisintegrant.

INTRODUCTION

With the increase demand of novel drug delivery, the fast disintegrating drug delivery system has become one of the mile stone of present investigations. Tablets produced by these technologies have sufficient mechanical strength, disintegration and dissolution profile. Recently fast dissolving formulation is popular as novel drug delivery systems because they are easy to administer and lead to better patient compliance. Paediatric and geriatric patient have difficulty in swallowing the conventional dosage forms these dosage forms dissolve or disintegrate in the oral cavity within a minute without the need of water or chewing.[1] Salivary glands which are present in the floor of the mouth under neath the tongue. They are also known as sublingual glands.[2] Sublingual administration of the drug means placement of

the drug under the tongue and drug reaches directly in to the blood stream through the ventral surface of the tongue and floor of the mouth. The drug solutes are rapidly absorbed into the reticulated vein which lies underneath the oral mucosa, and transported through the facial veins, internal jugular vein and braciocephalic vein and then drained in to systemic circulation.[3] fast dissolving tablets are also applicable when local action in the mouth is desirable such as local anesthetic for toothache, oral ulcers, cold sores, or teething. they do not require water for administration, thus are good alternative for travelers and for bed ridden patients. difficulty in swallowing is experienced by patients such as geriatric & pediatric patients, disabled and mentally ill.[4]

MATERIAL AND METHOD

Amlodipine besylate given by mylan laboratories, nashik. Crosscarmellose sodium given by BDR Pharma ltd., vadodara. The λmax of amlodipine besylate was scanned on UV visible spectrophotometer – Systronics 2201, Ahmadabad. other all excipients used from labs.

Preparation of Sublingual tablets

Each tablet containing 10mg of amlodipine besylate was prepared by using Direct compression technique. The superdisintegrants crosscarmellose sodium(2%, 4%, 6%) and Guargum (2%, 4%, 6%) were used in different proportion and in different combinations. All the ingredients were passed through sieve no.60 and kept in hot air oven at 60°C to make anhydrous and accurately weighed. The drug, superdisintegrant, mannitol, microcrystalline cellulose were mixed to improve drug distribution and content uniformity and triturated in mortar. After then talc and magnesium stearate were passed through sieve no 80 mixed and blended well with the previous mixture. Then the mixture was compressed using single punching machine to produce tablet weighing 120mg, six batches were prepared. Guargum was available commercially.[4]

Table1: composition sublingual tablet of amlodipine besylate.

Ingredient	Formulations					
	F1	F2	F3	F4	F5	F6
Amlodipine besylate	10	10	10	10	10	10
Guar gum	2	4	6	_	_	_
Crosscarmellose sodium	_	_	_	2	4	6
Manitol	80	78	76	80	78	76
Aspartame	3	3	3	3	3	3
Magnesium starate	1	1	1	1	1	1
Talc	3	3	3	3	3	3

Microcrystalline cellulose	21	21	21	21	21	21
TOTAL	120	120	120	120	120	120

Precompression parameters

1. Bulk density(BD)

Bulk density was determined by pouring gently 25 gm of sample through a glass funnel in to a 100 ml graduated cylinder. The volume occupied by the sample was recorded. Bulk density was calculated.[5]

$$\text{Bulk density (g/ml)} = \frac{\text{Weight of sample in gm}}{\text{Volume occupied by the Sample}}$$

2. Tapped density (TD)

It is the ratio of total mass of powder o the tapped volume of powder. The minimum volume(Vt) occupied in the cylinder and weight of powder blend (M) was measured. It was calculated by the formula.

Tapped density = Weight of powder (M)/tapped volume (Vt)

3. Angle of Repose (q)

It was determined by fixed funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height(h) was obtained. Radius(r) of the heap was measured and angle of repose was measured using formula.

$\tan(q) = h/r$

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

where, q is the angle of repose

h is the height in cms

r is the radius in cms

4. Carr's index/ % Compressibility

It indicates the powder flow properties. The simplest way for measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index. The value below 15% indicates a powder which gives rise to good flow properties whereas above 25% indicates poor flow ability which is calculated by following formula.

%C.I = TD-BD/TD x100

5. Hausner Ratio

It is an indirect index of ease of powder flow. Hausner ratio is the ratio of tapped density to bulk density. Lower the value of Hausner ratio better is the flow property. Powder with Hausner ratiless than 1.18, 1.19, 1.25, 1.3- 1.5 and greater the 1.5 indicate excellent, good, passable, and very poor, respectively. It is calculated by following formula.

Hausner ratio = TD / BD, Where, TD is the tapped density

BD is the bulk density

Lower hausner ratio(<1.25) indicates better flow properties than higher ones(1.25)

Postcompression parameters

1. Weight variation: The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. Twenty tablets were randomly selected from each formulation, individually weighed, the average weight and standard deviation was calculated.[6]

2. Hardness: The hardness of tablet is an indication of its strength. Measuring the force required to break the tablet across tests it. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation is determined by Monsanto hardness tester, Pfizer hardness tester etc.

3. Friability test: Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator is employed for finding the friability of the tablets. Weigh the 20 tablets from each batch and place in Roche friabilator that will rotate at 25 rpm for 4 minutes. Dedust the all tablets and weigh again. Weight loss should not mre than 1%. The percentage of friability can be calculated using the formula.[7]

% Friability = [(W1-W2)100]/W1

Where, W1= Weight of tablet before test, W2 = Weight of tablet after test.

4. Disintegration test: The USP disintegration apparatus contains six glass tubes that are “3 long, open at the top and held against 10” screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 liter beaker of

distilled water at 37± 2°C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

5. Wetting time: A piece of tissue paper folded twice was kept in a Petri dish (inter diameter 5.5cm) containing 6ml of purified water. The tabletwas placed on the tissue paper and allowed to wet completely. The time required for complete wetting of the tablet was then recorded.[8]

6. Uniformity of content: six tablet were finely powdered; quantity equivalent to 10mg of amlodipine besylate was accurately weighed and transferred to 100 ml volumetric flask containing 50ml of methanol. Solution were made up to volume, filtered, suitably diluted and estimated for amlodipine besylate contents at 239nm, using UV- visible spectrophotometer using methanol as blank.

7. In-Vitro dissolution test: In-vitro dissolution study is performed by using USP Type II Apparatus (Paddle type) at 50 rpm. Phosphate buffer pH 6.8, 900 ml is used as dissolution medium which maintained at 37±0.5°C. Withdraw aliquot of dissolution medium (10 ml) at specific time intervals (2 min) and filter. The amount of drug dissolved is determined by suitable analytical technique.[9]

8. Compatabiliy study by FTIR: The drug - excipients interaction were studied using FTIR. IR spectra for drug and powdered tablets were recorded in a Fourier transform infrared spectrophotometer with KBr pellets.[10]

RESULT

The present study was undertaken to formulate fast disintegrating tablet of amlodipine besylate with a view to deliver the drug in rapid manner. The objective of the study is to carry out the comparative invitro release of amlodipine besylate tablets which were prepared from two superdisintegrants one was natural (guargum) and other was synthetic(crosscarmellose sodium). Guargum have been used as disintegrant because of its tendency to swell in water. It showed good disintegration characteristics. So, here crosscarmellose sodium shows the best disintegrating property as compared to guar gum. In vitro study that was conducted showed that crosscarmellose sodium has better dissolution at 6% as compared to dissolution of guar gum at 6% as shown in table 11 as it releases the drug more than 90% in 60min. as compared to guar gum.

Precompression studies include the evaluation of tablet powder blend for the micromeritic properties like angle of repose, tapped density, bulk density, carr's index, hausner ratio. Their results were summarized in table no. 2.

Table 2: result of precompression parameters

Parameters	Formulation					
	F1	F2	F3	F4	F5	F6
Bulk density	0.54	0.52	0.53	0.53	0.54	0.54
Tap density	0.70	0.67	0.67	0.68	0.69	0.68
Carr's index	22.85	22.38	20.89	22.06	21.73	20.58
Hausnar ratio	1.29	1.28	1.26	1.28	1.27	1.25
Angle of repose	27.21	28.20	26.17	26.13	26.56	27.01

Amlodipine sublingual tablets were prepared by direct compression method. The compositions of the formulations are shown in the Table1. Table 2 shows the data obtained from the evaluation of tablet blend. All batches of the tablets were preliminarily evaluated for various physical parameters such as hardness, friability, drug content, wetting time, disintegration and dissolution which were reported in Table no 2. All above properties and value were near to boundary of standard limit. All the tablets maintained hardness in the range 4.51-3.19 kg/cm2. The loss in total weight of the tablets due to friability was in the range of 0.416-0.666%. The drug content in different formulation was highly uniform and in the range of 96-99%. Wetting time is used as an indicator of the ease of tablet disintegration and found to be 17-31sec. The result of In-vitro disintegration were within the prescribed limits and comply with the criteria for orally disintegrating tablets, the value were with 51-9sec. In vitro dissolution studies are shown in table 3 and fig. 1, 2 and 3. The concept of super disintegrant addition method proved to be beneficial in order to lower the disintegration time. The quicker disintegration time may be attributed to faster water uptake by the tablets. Dissolution profiles revealed that, after 20 minutes, formulations F1-F6 shows % Drug release of 91.71, 95.89, 97.99, 91.86, 98.03 97.96, 94.41, 98.52 and 99.59 respectively. Among all the formulations, F9 formulation shows better dissolution efficiency and rapid disintegration with release of 99.59% within 20Min.

Table 3: results of postcompression parameters

Parameters	Formulation					
	F1	F2	F3	F4	F5	F6
Hardness	4.51	4.12	3.81	3.90	3.43	3.19
Friability	0.416	0.583	0.541	0.458	0.583	0.666
Wt. variation	120±0.94	120±1.02	120±1.84	120±1.96	120±1.80	120±1.98

Content uniformity	96 ±1.78	98 ±0.81	98± 0.49	98± 1.21	99± 0.91	99 ±0.19
Disintegration time	51sec.	43sec.	30sec	19sec.	12sec.	9sec.
Wetting time	31sec.	25sec.	23sec.	26sec.	22sec.	17sec.

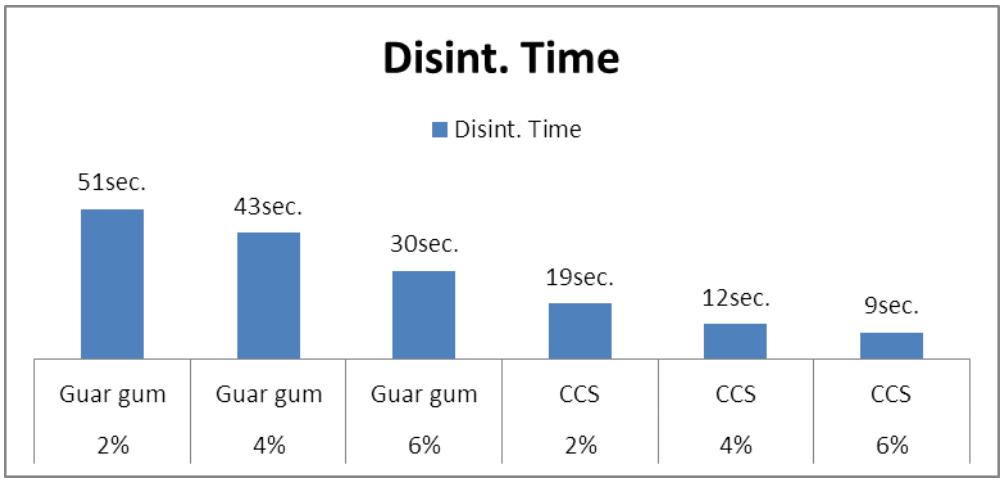

Figure1: column graph of comparative disintegration time of SLT by using natural and synthetic superdisintegrants.

***In-vitro* drug release study**

The *in-vitro* dissolution studies of all formulations (i.e.F1 to F6) were carried out in pH 6.8 phosphate buffer. The release of drug is largely depends upon the disintegration of tablet i.e. faster the disintegration of tablets, better and faster will be the release of drug. The drug release was found above 20-90% after 2 minutes. Formulation batch no. F1-F3 releases 95.78-98.02% of drug after 14 minutes, containing guar gum as a superdisintegrants (2%, 4%, 6%) It was found that disintegration time lower when conc. of superdisintegrants increases, hence more drug release was observed form the fast disintegrating sublingual tablet of amlodipine besylate. while as compare to guar gum formulation batch no. F4-F6 containing crosscarmellose sodium as a superdisintegrants (2%, 4%, and 6%) released 96.94-99.90% of drug after 14minutes. It was found that formulation containing crosscarmellose gives better and faster drug release than the guar gum containing formulation. The graphical representation of drug release study was given in fig. no.2.

Table 4: result of dissolution studies of formulation F1-F6.

Time in min.	Formulation					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
2	52.59	59.94	63.34	59.67	70.54	69.76
4	70.35	74.27	77.19	73.39	83.51	84.60
6	86.23	90.87	91.59	89.43	94.17	95.79

8	91.79	94.95	94.43	91.51	97.09	97.96
10	93.63	97.59	97.05	95.11	98.23	99.70
12	95.78	98.39	98.02	96.94	98.79	99.90

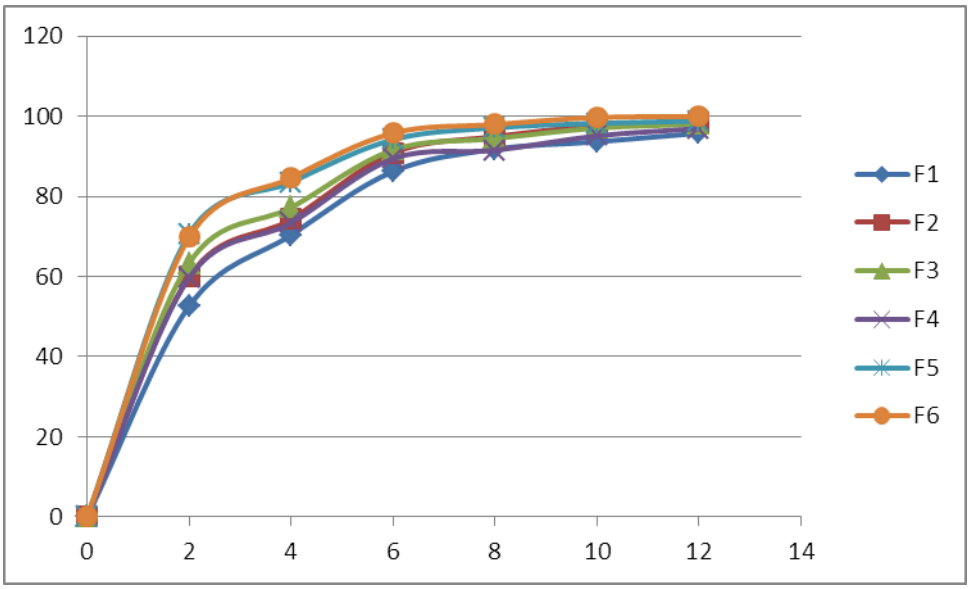

Fig2: in-vitro drug release profile of formulations F1-F6

Compatability study

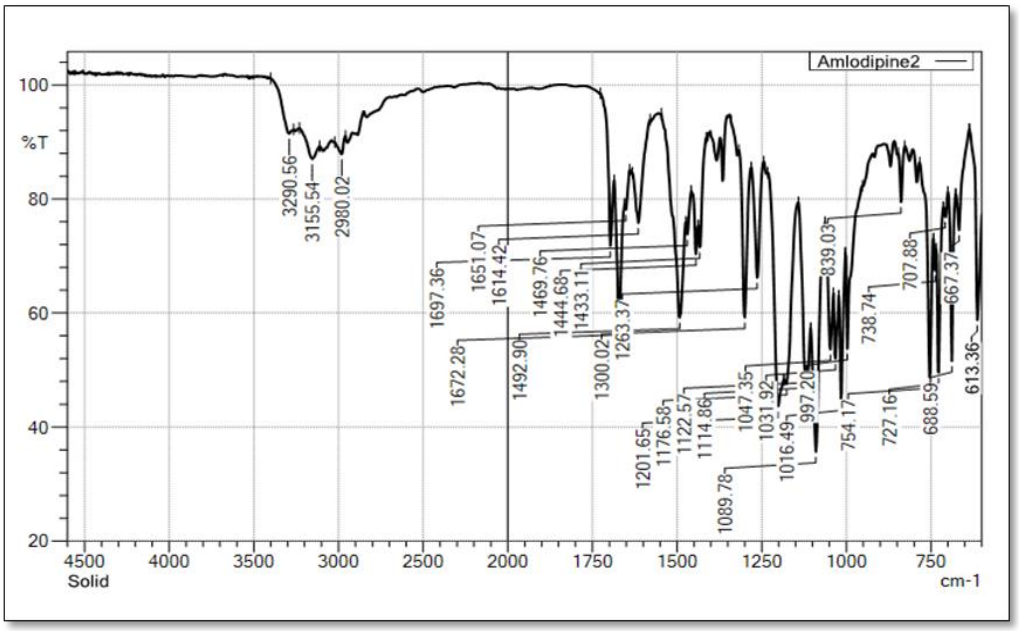

Figure3: FTIR spetra of amlodipine besylate

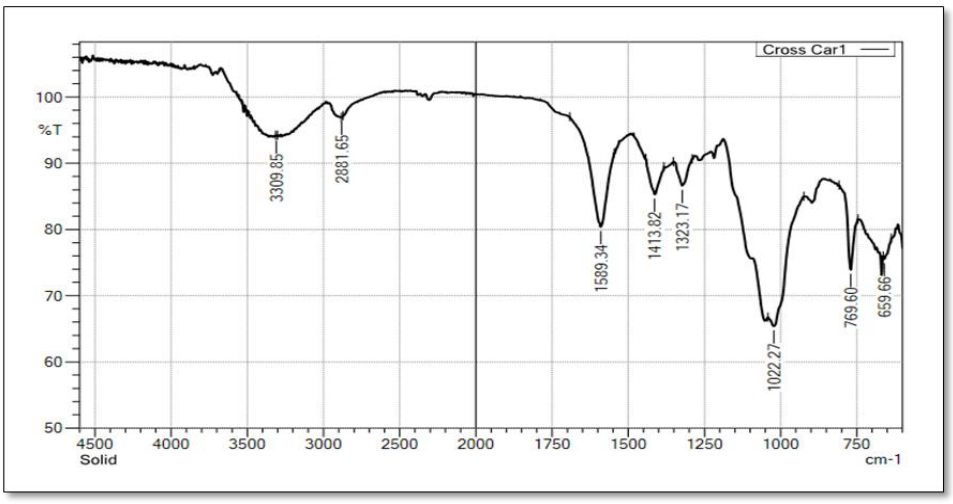

Figure: FTIR Spectra of crosscarmellose sodium.

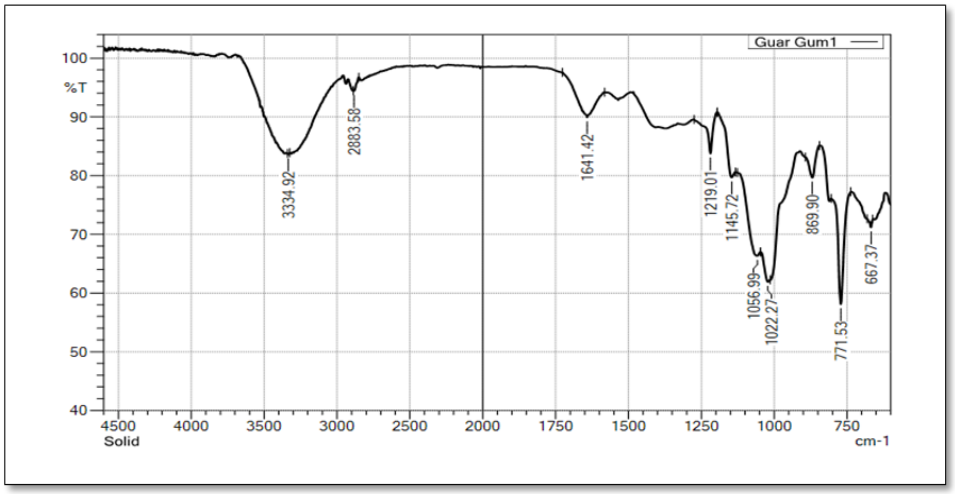

Figure5: FTIR spectra of guar gum

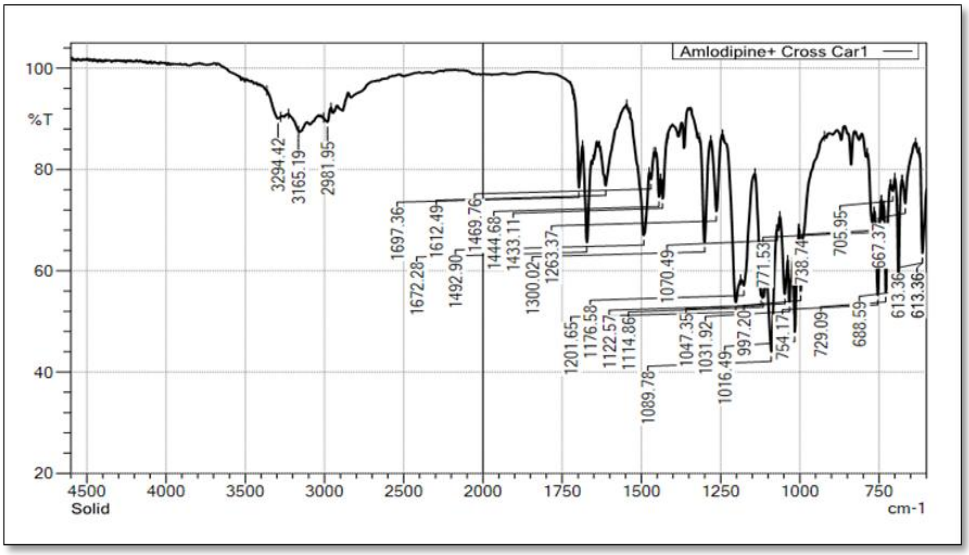

Figure 4: FTIRspectra of amlodipine+ crosscarmellose sodium.

Compatibility study by FTIR shows that there was no any compatability seen in FTIR spectra of drug and excipients.

CONCLUSION

This study involves preformulation studies, compatibility with excipients, formulation and evaluation of tablets. Literature review showed that amlodipine besylate is a antihypertensive drug. Preformulation study was done and batches of amlodipine were also prepared using guargum as a natural superdisintegrant and crosscarmellose sodium as synthetic superdisintegrant. Also micromeritic properties were calculated like bulk density, tapped density, angle of repose, hausners ratio. All the formulation had showed good blend properties. The tablets were prepared by using Direct compression technology. All the formulation disintegrated within 2 minutes. Crosscarmellose sodium shows the good disintegrated property. In vitro dissolution studies conducted for both guargum and CCS, table revealed that F6 is an optimized formulation that releases the drug above 90% within 12 min. as compared to F3 which is a Guar gum preparation. So, we can say that instead of using natural superdisintegrant use of synthetic ones like crosscarmellose sodium should be used.

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