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Formulation and development of fast disintegrating tablet of Nortriptyline hydrochloride

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ABSTRACT

The aim of the present work was to formulate mouth dissolving tablet of Nortriptyline hydrochloride. Nortriptyline hydrochloride is N-demethylated active metabolite of Amitriptyline and is tricyclic antidepressant. It has ability to inhibit the reuptake of serotonin and norepinephrine and act at beta adrenergic receptor. In the present work effect of different concentration of disintegrant was evaluated. All the formulation were evaluated for influence of characteristics of tablet mainly disintegration time and dissolution study. Polyplasdone XL-10 and sodium starch glycolate was used in different concentration as individually and in combination. Formulation containing SSG (10%) showed a rapid disintegration of tablet as compared to polyplasdone XL-10 in a concentration less than 5%. Formulation in which combination of both disintegrant F-7 (7.5 % SSG and 2.5 % Polyplasdone) was used, showed less disintegration time along with less wetting time.

Keywords: Nortriptyline, Superdisintegrant, Sodium starch glycolate, Polyplasdone, Tablet

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INTRODUCTION

Tablet formulation has been conveniently and practically use for long time [1]. However, problem like swallowing the tablet, dysphasia and hand tremor make it as inconvenient dosage form. Mouth dissolving tablet is one of the dosage form which improves the above problem [2]. Mouth dissolving tablet disintegrate in oral cavity within several seconds by saliva upon putting the tablet in mouth and can be taken without water [1]. Formulation and development of Nortriptyline HCl mouth dissolving tablet offer an alternative for other dosage form of Nortriptyline HCl (Capsule). Nortriptyline HCl is tricyclic antidepressant and used to treat mental disorder. It improved mood fillings of well-being, relieve anxiety and tension and increases energy level. It act by inhibiting the natural chemical (Neurotransmitters) in the brain. In the present study by formulating fast dissolving tablet an attempt was made with the aim to enhance drug release [3]. Effect of disintegrants at various concentrations on drug release and disintegration time was studied. The market survey revealed that there are no such types of formulation existing so it was thought to formulate fast dissolving tablet [4].

EXPERIMENTAL SECTION

Nortriptyline hydrochloride was a gift sample from Wockhardt Research Centre, Aurangabad. All the excipients including sucralose and strawberry flavor were also gift sample from Wockhardt Research Centre, Aurangabad.

1. Standard Calibration curve [5-6]**:**
Preparation of standard stock solution:
10 mg drug was weighed and transfer to volumetric flask. Volume was made up to 10 ml using pH 6.8 phosphate buffer (1000µg/ml), from that 1 ml of solution was taken and diluted up to 10 ml (100µg/ml)

Preparation of standard calibration curve:
For the preparation of standard calibration curve, concentration of 4–20µg/ml was prepared and absorbance was taken by using UV spectrophotometer (Varian) at λ max 239 nm.

Method validation by using UV spectrophotometer:
1. Linearity: Linearity of the analytical method is its ability to elicit test results which are directly proportional to analyte concentration in samples within a given range. To establish the linearity of the proposed method, various aliquots of the standard solution of the drug were prepared from stock solution and analyzed.

2. Accuracy: Accuracy of the proposed method was determined using recovery studies. The recovery studies were carried out by adding different amounts (80%, 100%, and 120%) of the standard drug to the pre-analyzed formulation. The solutions were prepared in triplicates and the % recovery was calculated

3. Precision: Precision study was carried out to ascertain the reproducibility of the proposed method. Repeatability was determined by preparing six replicates of same concentration of the sample and the absorbance was measured. Intraday precision study was carried out by preparing drug solution of same concentration and analyzing it at three different times in a day. The same procedure was followed for three different days to determine interday precision.

The result was reported as % RSD.
4. Specificity: Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically these might include impurities, degradation products, matrix, etc.

5. LOD and LOQ: Limit of detection (LOD) is the lowest amount of analyte in the sample that can be detected. Limit of quantification (LOQ) is the lowest amount of analyte in the sample that can be quantitatively determined by suitable precision and accuracy. LOD and LOQ is calculated by using following formula

LOD = 3.3* S.D. / 100 ---------- equation 1

LOQ = 10 * S.D. / 100 ---------- equation 2

6. Robustness: Analysis was carried out at two different temperatures, room temperature and at 18^0C to determine the robustness of the method and the respective absorbance was measured.

7. Ruggedness: Ruggedness was determined by carrying out analysis by two different analysts and the respective absorbance was noted and the result was indicated as % RSD.

2. Drug-Excipient Compatibility Study:
The evaluation of drug-excipient compatibility is depending on inherent property of drug as well as excipients. Drug excipient compatibility study is an investigation of physicochemical property of drug substances alone and in combination with excipients [5-6].

Procedure:
API with excipients was mixed in appropriate ratio as per their functionality as shown in table no.1. The blend was subjected to 40°C ± 2°C/75% ± 5% RH 1 month. Analysis was carried out using Infrared spectroscopy (GASCO FTIR - 4600), and UV spectroscopy (Varian).

Table No.1: Drug excipient compatibility study

Ingredients	Ratio
API	1:1
API : Prosolved SMCC HD-90	1:1
API : Pearlitol SD-200	1:1
API : Ceolus – 711	1:1
API : Polyplasdone XL-10	1:1.5
API : Sodium starch glycolate	1:1.5
API : Magnesium stearate	1:1
API : Aerosil – 200	1:0.1
API : Strawberry flavor	1:0.1
API :Sucralose	1:0.1

3. Preparation of Fast Dissolving Tablet of Nortriptyline hydrochloride:

Tablet containing Nortriptyline HCl was prepared by direct compression. Tablet was directly compressed by using API along with excipients (filler, disintegrating agent, sweetener, flavors etc.). Drug, filler (Prosolved SMCC HD-90, Pearlitol SD-200, Ceolus-711) and disintegrating agent i.e. SSG (10%, 7.5%, 5%), Polyplasdone XL-10 (10%, 7.5%, 5%) were shifted through sieve no.40. Aerosil-200 was shifted through sieve no.40. Blend were transferred in blender for 5 min. Strawberry flavor and sucralose are weighed and pass through sieve no.40 and transfer in blender for 3 min. Magnesium stearate were weighed and pass through sieve no.60, then was transfer in blender and allowed to stand for 3 min. Formulas are as shown in table no 2.

Blend was removed from the blender and compressed the tablet by using 7 mm punch tooling (plain on both side) by using 8 station compression machine (Cadmac compression machine).

Table No 2: Formulation of mouth dissolving tablet of Nortriptyline HCL

Sr. No.	Name of Ingredients	Formulations (mg/tab)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Nortriptyline HCL	10	10	10	10	10	10	10	10	10
2	Prosolved SMCC HD-90	20	20	20	20	20	20	20	20	20
3	Pearlitol SD-200	40	42.5	45	45	42.5	40	40	40	40
4	Ceolus – 711	15	15	15	15	15	15	15	15	15
5	Polyplasdone XL-10	10	7.5	5	*	*	*	2.5	5	7.5
6	Sodium starch glycolate	*	*	*	5	7.5	10	7.5	5	2.5
7	Magnesium stearate	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
8	Aerosil – 200	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
9	Strawberry flavor	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
10	Sucralose	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight in mg/Tablet		100	100	100	100	100	100	100	100	100

Evaluation Parameter:

Pre compression parameter:

Bulk Density: Bulk density was determined by measuring the known mass (approximately 100 gram were weighed) of powder sample that has been pass through screen (sieve no 60) into graduated cylinder or through a volume measuring apparatus into a cup. Then bulk density was calculated using following formula.

$$\text{Bulk density (g / mL)} = \frac{\text{Weight of the sample (g)}}{\text{Volume of sample (mL)}} \quad \text{---------- equation 3}$$

Tapped Density: Tapped density is a limiting density attained after tapping down usually in a device that lift and drops a volumetric measuring cylinder containing the powder a fixed distance.

Mechanically tap the cylinder containing sample and allowing it to drop under its own weighed using suitable mechanical tapped density tester that provide fixed drop of 14±2 mm at nominal rate of 300 drops per unit. Tapped the cylinder 500 times initially and tapped volume was measure to the neared. Additional 750 tapping was carried out and tapped volume was measure, difference between two value was find to be less than 2 % [7] .

$$\text{Tapped density (g / mL)} = \frac{\text{Weight of tapped sample (g)}}{\text{Volume of sample (mL)}} \quad \text{---------- equation 4}$$

Compressibility Index and Hausner's Ratio: Compressibility index and Hausner's ratio are measure of compressibility of powder. As such, they are measures of the relative importance of interparticle interactions, in a free flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index and the Hausner's Ratio.

$$\text{Compressibility index} = 100(V_0 - V_f) \quad \text{---------- equation 5}$$

$$\text{Hausner's Ratio} = V_0 / V_f \quad \text{---------- equation 6}$$

Post compression parameter:
Weight variation- 20 tablets were randomly selected from each batch individually weighed. The average weight of these selected tablets was calculated.

Hardness- Tablet crushing strength is force required to break the tablets and was done by using Erweka tester. Hardness was calculated in Newton's [8].

Thickness- Thickness of tablet is the measure in micrometer by using Vernier caliper. It gives idea about variation between tablets. Tablet thickness within a ± 5% variation of standard value.

Friability testing- Tablet friability test was measured using a Roche friability apparatus (USP) at 25 rpm for 4 min. A sample of tablets corresponding 6.5 gm as per USP were taken for the study.

Disintegration time- This test is carried out to determine whether tablet disintegrate within prescribe time or not. Disintegration time was determined by disintegration test apparatus.

Wetting time- Wetting time of mouth dissolving tablet is another important parameter, which need to give an insight into disintegration properties of tablets. Lower wetting time indicate quicker disintegration properties of the tablets. For this test two circular tissue paper of 10 mm of water containing methylene blue dye was added to petri dish. Tablet was then carefully placed on surface of tissue paper. The time required for water to reach upper surface of the tablet was noted as a wetting time.

***In- vitro* Dissolution Testing-** Dissolution study was performed by using dissolution test apparatus **(**Electro lab). Dissolution study was conducted for all the formulation by using USP apparatus type II containing 900 ml 6.8 pH phosphate buffers at 50 rpm and 37^0C temperature. Three tablets were use for each test. Aliquots of dissolution medium (5 ml) were withdrawn at specified interval of time and analyzed for drug content by measuring the absorbance at 239 nm. The volume withdrawal at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent of drug release was calculated and plotted against time.

F1 (dissimilarity) and F2 (similarity) factor calculation:
Similarity and dissimilarity factor was carried out for batch F7 using marketed formulation PAMELOR 10 mg cap containing Nortriptyline HCl using BIT software and result was noted.

RESULTS AND DISCUSSION

Standard calibration curve:

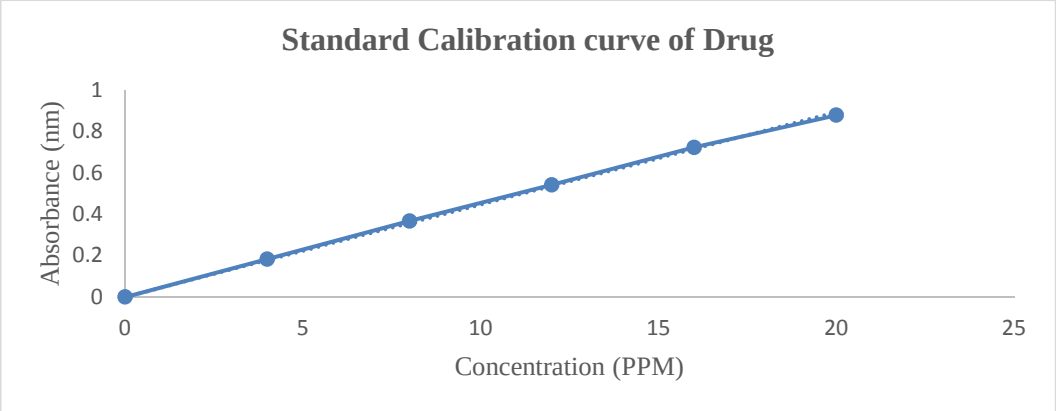

Figure 1: Standard calibration curve

Figure 1 shows the calibration curve of Nortriptyline HCl. It followed Beers- Lamberts law with equation

y=0.0447x and R^2=0.998

Method validation by using UV spectrophotometer:
1. Linearity:
From table no.3 it can be seen that linearity of all the concentration was observed.

Table No 3: Linearity by using UV spectrophotometer

Concentration	0	4	8	12	16	20
Absorbance	0	0.182	0.352	0.549	0.719	0.869
	0	0.185	0.363	0.558	0.725	0.881
	0	0.186	0.359	0.561	0.729	0.889
Mean	0	0.184333	0.358	0.556	0.724333	0.879667
S.D.	0	0.002082	0.005568	0.006245	0.005033	0.010066
RSD	0	1.129294	1.555241	1.123201	0.694877	1.144348

2. Accuracy:
From table no. 4 it can be concluded that the recovery study was carried out successfully by using UV spectrophotometer.

Table No 4: Accuracy study by using UV spectrophotometer.

Recovery level	Amount from formulation	Amount from Standard	Total Amount	Absorbance	Average	Amount Recover	% Recovery
80%	0.8 ml	1 ml	1.8 ml	0.79	0.788	17.81	98.94
				0.783			
				0.791			
100%	1.0 ml	1 ml	2.0 ml	0.875	0.87967	19.64	98.2
				0.884			
				0.88			
120%	1.2 ml	1 ml	2.2 ml	0.976	0.98033	21.91	99.59
				0.984			
				0.981			

3. Precision: Interday and intraday precision study was done carefully by using sample having concentration of 12µg/ml and result was found to be within a limit. Interday S.D was found to be 0.00864 and % RSD was found to be 1.54 %. Intraday S.D was found to be 0.00354 and % RSD was found to be 0.630%.

4. Specificity:
Specificity was done successfully, result was within a limit. S.D. was found to be 0.00871 and % RSD 1.54 of sample having concentration of 12µg/ml.

5. LOD and LOQ:
LOD was found to be 0.460 and LOQ 1.39 indicate that result obtain was in the limit.

6. Robustness:
Analysis was carried at two different temperature and result were note down. At normal temperature S.D. and % RSD was found to be 0.0038 and 0.440 respectively and at 18^0C S.D. and % RSD was found to be 0.0052 and 0.601 respectively.

7. Ruggedness:
Analysis of the same sample and at same concentration was done by two people. S.D. and % RSD of analyst 1was found to be 0.0011and 0.638 & S.D. and % RSD of analyst 2 was found to be 0.00186 and 1.0.

COMPATIBILITY STUDY:
Peak identification:
Following are the peak observed for drug which matches with the peaks reported in IP 1996 for drug [9]. Peak obtain are 3457 cm $^{-1}$, 3168 cm $^{-1}$,3127 cm $^{-1}$, 3054 cm $^{-1}$, 2388 cm $^{-1}$, 2145 cm $^{-1}$, 1908 cm $^{-1}$,1943 cm $^{-1}$, 1701 cm $^{-1}$, 1649 cm $^{-1}$, 1623 cm $^{-1}$,1583 cm $^{-1}$,1474 cm $^{-1}$.

After 1 month study at 40°C ± 2°C/75% ± 5% RH , peak observed after IR characterization as seen in figure 2, it was concluded peak observed of all excipients-drug are identical to drug and does not showed any interaction with drug hence study confirm compatibility of drug with excipients [10].

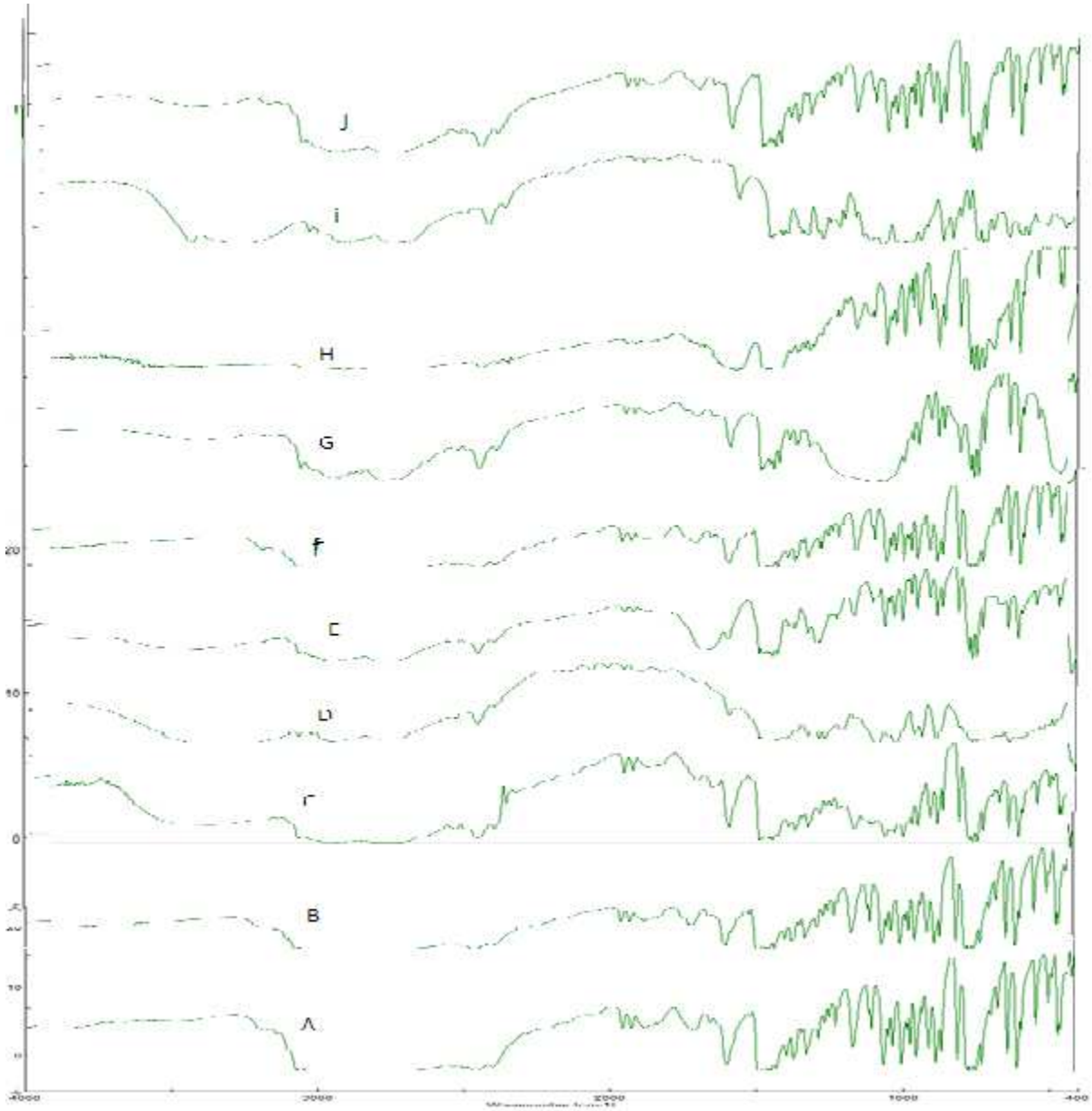

Figure 2: Compatibility study by using IR of drug along with excipients

A: Nortriptyline HCL, B: drug + formulation, C: drug + Prosolved SMCC HD-90, D: drug +Pearlitol SD-200, E: drug + ceolus-711, F: drug + polyplasdone XL-10, G: drug + sodium starch glycolate, H: drug + aerosol-200, I: drug + magnesium stearate, J: drug + sucralose, K: drug + strawberry flavor.

Pre -compression Parameter Evaluation:

Table No 5: Evaluation Parameter of Blend Powder

Formulation	Bulk Density	Tapped Density	Hausner's Ratio	Carr's Index	Angle of Repose (Degree)
F1	0.43 g/ml	0.60 g/ml	1.39	29.79%	25.43
F2	0.43 g ml	0.58 g/ml	1.33	24.95%	26.41
F3	0.44 g/ml	0.57 g/ml	1.285	22.06%	25.50
F4	0.45 g/ml	0.57 g/ml	1.25	20.39%	24.32
F5	0.47 g/ml	0.54 g/ml	1.15	13.38%	27.10
F6	0.46 g ml	0.52 g/ml	1.12	11.38%	26.40
F7	0.45 g/ml	0.56 g/ml	1.24	19.64%	25.90
F8	0.46 g/ml	0.57 g/ml	1.23	19.29%	26.30
F9	0.48 g ml	0.58 g/ml	1.2	17.24%	25.75

Bulk density and Tapped density of all formulation was within the limit and showed good flow characteristic of blend. Carr's Index and Hauser's Ratio is the measure of compressibility of powder. Formulation containing

Polyplasdone XL-10 showed poor compressibility (F1,F2,F3),as polyplasdone is hygroscopic it forms the gel like structure and creates problem in flow property of bulk powder but formulation containing sodium starch glycolate showed good compressibility of powder blend (F6, F7, F8, F9).

Post compression Parameter Evaluation:

Table No 6: Evaluation Parameter of Tablets

Formulation	Weight variation (mg)	Friability (%)	Hardness (N)	Thickness (MM)	Disintegration Time (Sec)	Wetting Time (Sec)	% Cumulative Drug Release in 30 Min
F1	98.0	0.6	25.0	3.5	33.0	43.0	79.8
F2	99.0	0.8	28.0	3.5	38.0	49.0	81.2
F3	100.0	0.5	27.0	3.5	40.0	55.0	82.9
F4	101.0	0.5	30.0	3.3	20.0	23.0	89.7
F5	100.0	0.5	35.0	3.1	16.0	19.0	97.7
F6	100.0	0.2	33.0	3.2	13.0	15.0	98.8
F7	101.0	0.5	35.0	3.2	11.0	16.0	98.7
F8	99.0	0.6	38.0	3.0	19.0	21.0	98.0
F9	98.0	0.5	36.0	3.1	27.0	25.0	96.9

Weight variation and % friability of all formulation was found to be within a limit. % Friability is not more than 1 % and weight variation limit according to USP is 10% and as per IP is found to be 7.5 %. Hardness alters the drug release pattern of dosage form and hence hardness and thickness play a crucial role in drug release. Formulation containing SSG (10%, 7.5%) with high hardness does not have any impact on the drug release characteristic of tablet (F5, F6). Due to presence of hydrophilic carboxy methyl group in sodium starch glycolate chemical structure, it allowed water to penetrate the molecule and polymer become cold water soluble and swelling results in fast disintegration of tablets [6, 11-12]. With increasing the concentration of SSG (F6, 10%) there was increase in disintegration time but comparatively less than other formulation in which Polyplasdone XL-10 was used even at higher concentration

F1, F2, F3, and F4 showed high wetting time and disintegration time. (Polyplasdone XL-10 is water insoluble disintegrants and showed capillary action) SSG showed concentration dependent results of disintegration time and wetting time in F5, F6 and F7. The formulation in which combination of disintegrants were used (7.5% SSG and Polyplasdone XL-10 2.5%) showed good result.

Drug Release Profile of Drug:

Drug Release profile of All Batches:

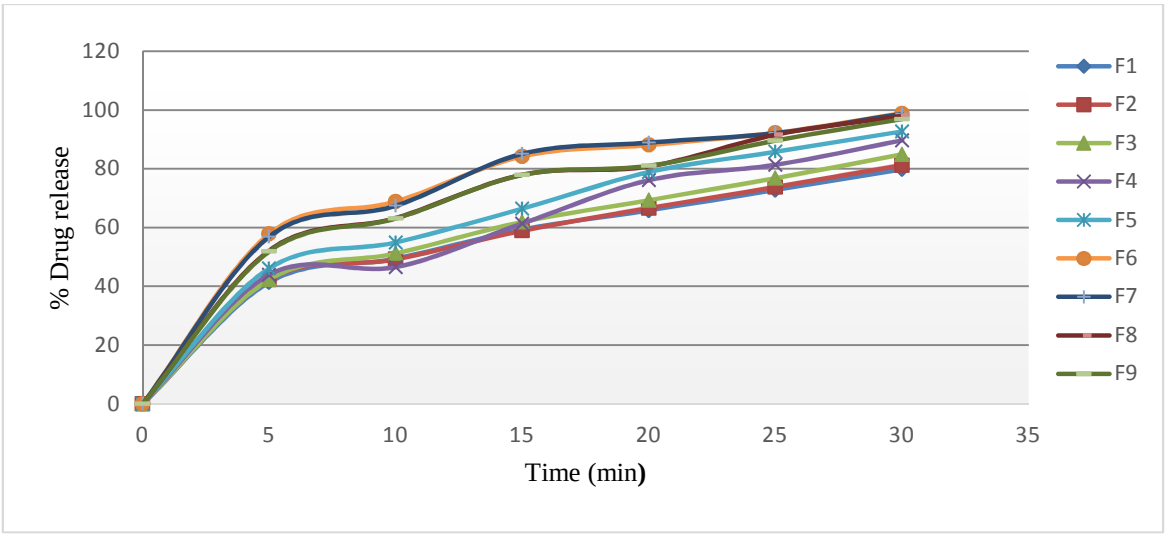

Figure 3: Percent drug release profile of all batches

From figure.3 it was observed that batch F7 showed better result than other formulation.

Drug release profile of batch F6, F7 and Marketed dosage form (PAMELOR 10 mg cap)-

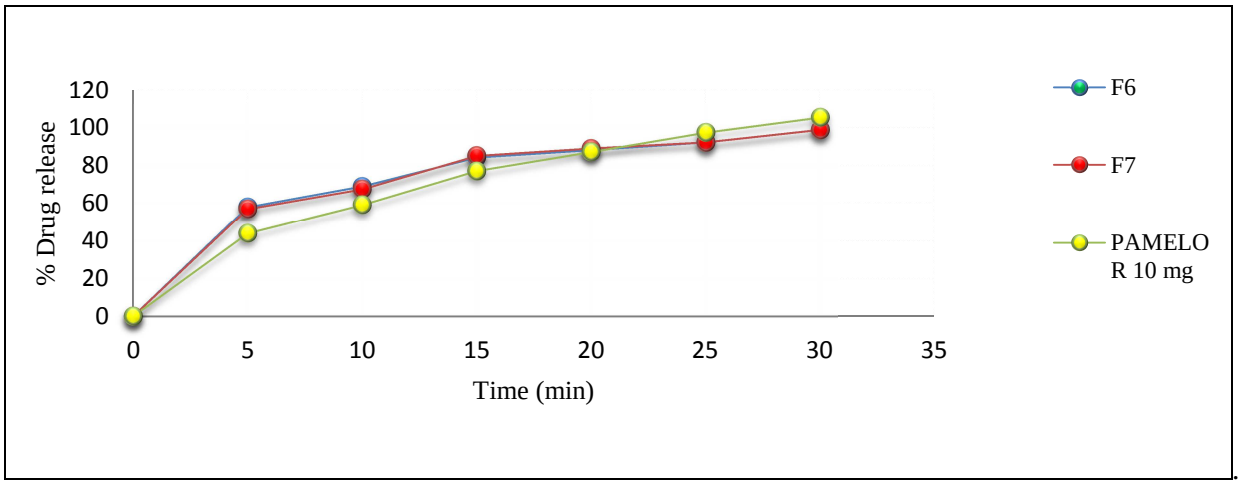

Figure 4: % Drug Release Drug release profile of F6, F7 and Marketed dosage form (PAMELOR 10 mg cap)

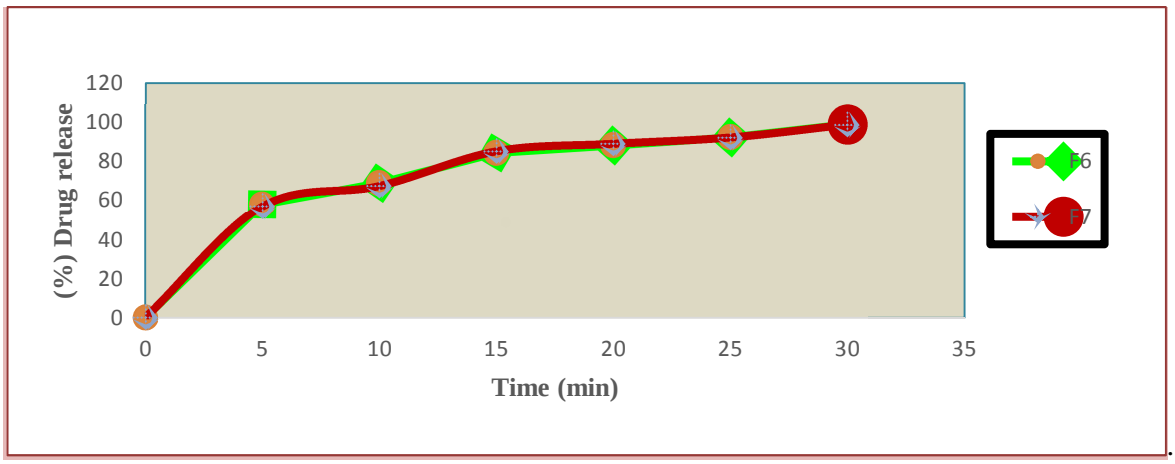

Figure 5: % Drug Release Profile of batch F6 and F7

F1 (dissimilarity) and F2 (similarity) calculation:

F1 calculates the percent difference between the two dissolution profiles at each time point and is a measurement of the relative error between the two curves. F2 is the comparison of closeness of two comparative formulations. Similarity factor of 50–100 ensure sameness of product dissimilarity factor of 0–15 ensure that minor difference between two product

From similarity and dissimilarity calculation by BIT software using batch F7 and marketed product i.e. PAMELOR 10 mg cap, F1 was found to be 09 and F2 was found to be 56. From the results it can be said that this formulation gives same drug release and showed better results comparable to marketed product.

CONCLUSION

From the results it can be concluded that sodium starch glycolate when used in combination with polyplasdone at a concentration of 7.5 and 2.5 % concentration showed better disintegration. F7 showed similar drug release profile when compared with marketed product i.e. PAMELOR 10 mg capsule. From F1 and F2 calculation it was concluded that this formulation also showed equivalent drug release profile when compare with PAMELOR 10 mg cap.

Acknowledgements

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