Research Article

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International Journal of Pharmaceuticals and Health care Research

ISSN: - 2306 – 6091

FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF THEOPHYLLINE

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Abstract

The main aim of present study is to formulate and evaluate orodispersible tablets of Theophylline. The demand for orodispersible tablets has been growing during the last decade, especially for the geriatric and pediatric patients who have been swallowing difficulties. Theophylline is a bronchodilator, which is used in the treatment of bronchial asthma. In the present work, 9 formulations of orodispersible tablets of theophylline (f1 to f9) are prepared using three different super disintegrants namely crosspovidone, croscarmellose sodium and sodium starch glycolate by direct compression method. The final blend of drug and excipients were evaluated for powder flow properties, bulk density, tapped density, compressibility index and Hausner's ratio. All the formulations were evaluated for weight variation, disintegration time, hardness, dissolution study, dispersion time, friability, drug content, wetting time and water absorption ratio. Formulation f3 showed the lowest dispersion and disintegration time and more water absorption ratios. Invitro dissolution studies revealed that formulation f3 showed 97.6% drug release at the end of 20 minutes. Therefore, overall results indicated that crosspovidone used formulation (F3) is a better one which satisfied all the criteria for orodispersible tablets of theophylline.

Keywords: Bronchial asthma, Direct compression, Orodispersible tablets, Theophylline, Superdisintegrant.

Introduction

Over a decade, the demand for development of orally disintegrating tablets (ODTs)has enormously increased as it has significant impact on the patient compliance. Orally disintegrating tablets offer an advantage for populations who have difficulty in swallowing. It has been reported that Dysphagia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting and motion sickness complications. ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population[1]

Orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapimelts. However, of all the

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above terms, United States pharmacopoeia (USP) approved these dosage forms as ODTs. Recently, European Pharmacopoeia has used the term orodispersible tablet for tablets that disperses readily and within 3 min in mouth before swallowing.[2]

United States Food and Drug Administration (FDA) defined ODT as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for ODTs generally ranges from several seconds to about a minute.[3] The main aim of present study is to formulate and evaluate orodispersible tablets of Theophylline using different superdisintegrants.

Materials and methods

The materials like Theophylline, crosspovidone, croscarmellose sodium, sodium starch glycollate, microcrystalline cellulose, sodium saccharin are purchased from Drugs India, Hyderabad. The other materials like starch, magnesium stearate, taic and mint are obtained from Ratnam Institute of pharmacy, pidathapolur, Nellore district, AP.

Preparation method

The Theophylline oroidspersible tablets are prepared by using direct compression method. . A total of nine formulations (F1toF9) of Theophylline orodispersible tablets were prepared using three superdisintegrants namely Croscarmellose sodium, Crospovidone and Sodium Starch Glycolate with three different concentrations(80mg, 100mg, 120mg) All the ingredients were passed through sieve no. 44 separately and collected. The drug, and microcrystalline cellulose were mixed uniformly with gentle trituration using mortar and pestle to get a uniform mixture. Required quantity of superdisintegrant and aspartame were taken for each specified formulation and mixed with the above mixture.Then binder starch is added. Finally magnesium stearate,talc and menthol were added and mixed well. The mixed blend of drug and excipients were compressed using 7 mm punch on 10 stations “B” Tooling Rotatory Tablet Punching Machine to produce convex faced tablets, weighing 450 mg each.[4]

Table No. 01: Formulation of orodispersible tablets of Theophylline

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Theophylline	100	100	100	100	100	100	100	100	100
Crosspovidone	80	100	120	-	-	-	-	-	-
Croscarmellose Sodium	-	-	-	80	100	120	-	-	-
Sodium starch Glycollate	-	-	-	-	-	-	80	100	120
Microcrystalline cellulose	175	155	135	175	155	135	175	155	135
Starch	50	50	50	50	50	50	50	50	50
Sodium saccharin	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5
Magnesium stearate	9	9	9	9	9	9	9	9	9
Talc	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Mint	9	9	9	9	9	9	9	9	9
Total weight	450	450	450	450	450	450	450	450	450

All the ingredients are taken in mg

Preformulation studies

Angle of Repose: Angle of repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (ɵ) was calculated using the formula.[5]

$$ɵ = \tan^{-}[h/r]$$

Bulk density: Apparent bulk density (ρb) was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of the powder (M) was determined. The bulk density was calculated using the formula.[5]

$$ρb = M/V$$

Tapped density: The measuring cylinder containing a known mass of blend was tapped for a

fixed time. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρt) was calculated using the formula:[5]

$$\rho t = M/ Vt$$

Compressibility index: Compressibility index I is calculated as follows:

$$I = V0-Vt/ V0\times 100$$

Where V0 is the bulk volume

Vt is the tapped volume.

The value below 15%indicates a powder with usually give rise to good flow characteristics where as above 25% indicate poor flowability.[5]

Haussner's ratio: Haussner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula:[5]

$$\text{Haussner's ratio} = \rho t/\rho b$$

ρt= tapped density ρb= bulk density

Lower Haussner's ratio (<1.25) indicates better flow properties than higher ones(>1.25).

Infrared spectroscopy study[5]: The study was carried out to determine the molecular structure serving as an identification test to ascertain the purity of the molecule. IR spectroscopy was obtained by a FTIR spectrophotometer using a scanning range of 400 - 4000cm-[1].

Evaluation studies

Hardness: Hardness or tablet crushing strength (Fc); the force required to break a tablet in a diametric compression was measured using a MONSANTO tablet hardness tester.[5]

Friability: Friability of tablets was determined using Roche friabilator (USP). Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions at 25 rpm. Tablets were dedusted using a soft muslin cloth and reweighed.[5]

$$\text{Percent friability} = [\text{initial wt-finalwt/ initial wt}] \times 100$$

Weight variation: Twenty tablets were randomly selected from each batch, individually weighed, the average weight and standard deviation of 20 tablets was calculated.[5]

Drug content: Twenty tablets were weighed and powdered. An amount of the powder equivalent to 100 mg of Theophylline was dissolved in 100 ml of pH 6.8 phosphate buffer, filtered, diluted suitably and analyzed for drug content at 270 nm using UV-Visible spectrophotometer.[6]

***In vitro* dispersion time**: Tablet was added to 10 ml of phosphate buffer solution (pH 6.8) at 37± 0.5°C, time required for complete dispersion of a tablet was measured.[5]

Wetting time: A glass petridish was partially filled with water and a tablet was placed on the surface of a band of filter paper supported on a glass slide. The uptake of water occurred from the lower surface of the tablet. The time required for water to reach the center of the upper surface of the tablet was noted as wetting time.[5]

Water absorption ratio: A piece of tissue paper folded twice was placed in a small petridish containing 6ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R was determined using the following equation:[5]

$$R= 100\times Wa –Wb / Wb$$

Where,

Wb is weight of tablet before water absorption and Wa is weight of tablet after water absorption.

***In-Vitro* disintegration time:** The test was carried out in a disintegration apparatus using distilled water as disintegration medium (at 37° C ± 0.5° C). A tablet was placed in each of six tubes of the apparatus and one disc was added to each tube. The time taken for complete disintegration of the tablet with no mass remaining in the apparatus was measured in seconds.[4]

***In Vitro* dissolution studies**

In-vitro dissolution studies for all the formulated tablets of Theophylline was carried out using USP II paddle method at 50 rpm in 900 ml of pH 6.8 buffer solution as a dissolution medium. The dissolution medium was maintained at 37±0.5°C. 5ml of sample was withdrawn at 5 minute time interval up to30 minutes. 5 ml of buffer solution (pH 6.8) was replaced to maintain the constant volume throughout the experiment. The samples were suitably diluted and the percentage of drug released from each formulation was measured at 270 nm using UV–visible Spectrophotometer.[4]

Stability study

Accelerated stability study was carried out as per ICH guideline 'Q1E Evaluation for stability Data'[8] using Ostwald stability chamber for best formulation the stability study was carried out at room temperature as well as different accelerated temperature and humidity conditions for a period of three months. The conditions were modified as 25°C/60%RH, 40°C/70%RH, 60°C/80%RH for every month i.e. 1st, 2nd and 3rd month respectively. Tablet samples were evaluated after 1st, 2nd and 3rd month for drug content as well as subjected for the *In vitro* drug release study. All the parameters have not shown any much variation when compared to the initial data. The *In vitro* dissolution was carried out for three months at the interval of one month.

Results and discussion

The present study is about formulation and evaluation of orodispersible tablets of Theophylline. It is subjected to various preformulation studies like Angle of repose, Bulk density, Tapped density, Carr's index and Haussners ratio. The results obtained were within the acceptable limit. Results data are tabulated in Table 2. Theophylline was subjected to Drug-Excipient compatibility studies with various excipients like crospovidone, croscarmellose sodium, sodium starch glycolate. The mixtures have shown no significant changes in the functional groups and colour changes. FTIR spectra are shown in Figure 1, 2 and 3. This indicates there were no significant interactions between drug and excipients. The tablets were formulated by using direct compression method. Then the tablets were subjected to evaluation parameters. The hardness values are found to be in the range of 3.2±0.263kp to 4.2±0.352kp. The friability values for all formulations are in the range of 0.56 ±0.023% to 0.79±0.052%. All the values are within the specified limits. The weight variation values for all the formulations are in the range of 447 ±1.3mg to 456±0.8mg. The in vitro dispersion time values for all the formulations are in the range of 29±0.9 sec to 45±1.2 sec. The values of wetting time for all the formulations are within the range of 52±0.12 sec to 69±0.35sec. The water absorption ratio values for all the formulations are within the range of 81±0.96 to 98±0.54. The in vitro disintegration time values for all the formulation values are within the range of 30±0.5 sec to 42±0.7 sec. The drug content for all the formulations are found to be in the range of 89±0.49% to 105±0.52%. The dissolution studies reveal that F3 formulation has shown 97.6% of drug released in just 20min. Results obtained in evaluation of tablets are given in Tables 3 and 4.

Stability studies were carried out for formulation F3 as per ICH guidelines. Formulation showed good stability and the values were within permissible limits. The residuals obtained from the calculated values are shown in Figure 5. The predicted shelf life was shown in Figure 6. The data of time versus cumulative percentage drug release profile are given in Table 5 and release pattern were shown in Figure 4.

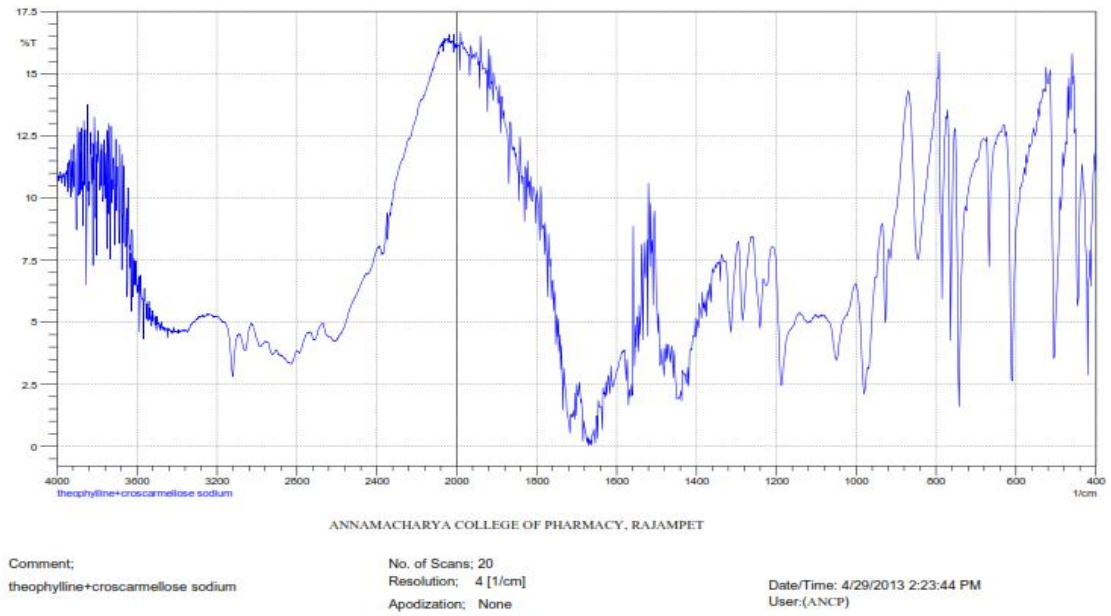

Fig. No. 01: FTIR spectrum of Theophylline and Croscarmellose sodium

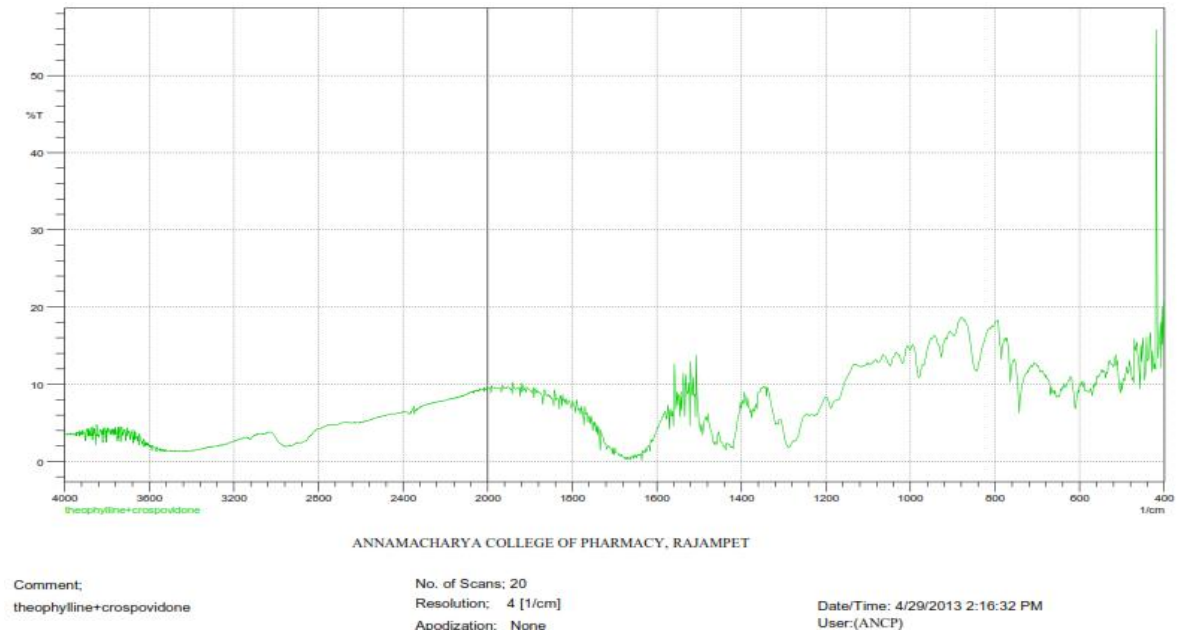

Fig. No. 02: FTIR spectrum of Theophylline and Crospovidone

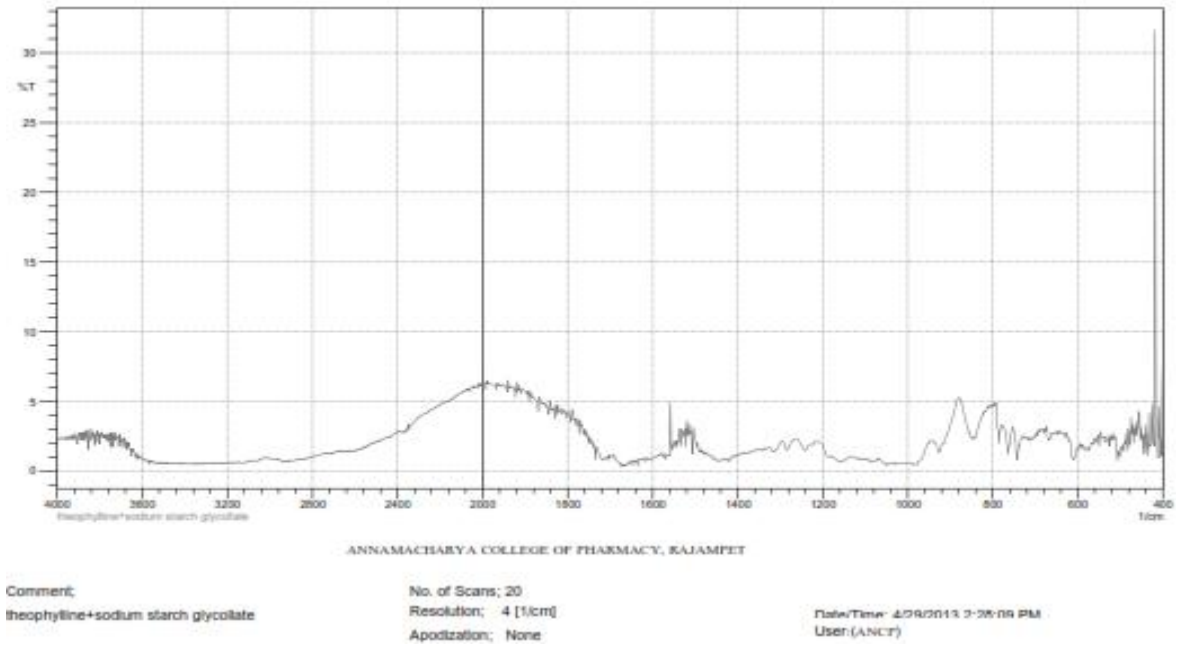

Fig. No. 03: FTIR spectrum of Theophylline and Sodium starch glycolate

Table No. 02: Preformulation Results

Formulation	Angle of repose(◦)	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Carr's index(%)	Haussner's ratio
F1	42◦71±0.1	0.44±0.002	0.58±0.045	24.4±0.1	1.31±0.008
F2	38◦61±0.5	0.4±0.005	0.55±0.026	28±0.4	1.38±0.002
F3	48◦81±0.6	0.41±0.004	0.58±0.025	29.1±0.5	1.39±0.005
F4	43◦21±0.4	0.5±0.006	0.66±0.058	25±0.8	1.33±0.008
F5	39◦51±0.3	0.42±0.009	0.54±0.063	24±0.7	1.35±0.004
F6	43◦51±0.2	0.55±0.008	0.64±0.047	26±0.9	1.4±0.006
F7	45◦31±0.1	0.45±0.004	0.57±0.068	27.5±0.6	1.42±0.009
F8	47◦21±0.8	0.48±0.008	0.59±0.087	28.8±0.5	1.45±0.008
F9	46◦21±0.7	0.45±0.007	0.57±0.098	25.3±0.3	1.36±0.004

All values are mean±SD, n=3

Table No. 03: Physicochemical evaluation data of orodispersible tablets of Theophylline

Formulation code	Weight variation	Hardness	Friability	In vitro dispersion time (sec)
F1	450±0.6	3.3±0.732	0.56±0.023	35±1.2
F2	452±0.5	3.5±0.692	0.67±0.012	30±1.3
F3	450±0.4	3.2±0.263	0.72±0.015	29±0.9
F4	456±0.8	3.3±0.593	0.54±0.053	32±1.5
F5	449±1.2	3.6±0.892	0.57±0.032	36±0.8
F6	453±0.5	4±0.123	0.62±0.055	40±0.6
F7	447±1.3	4.2±0.352	0.75±0.025	39±0.5
F8	451±0.9	3.9±0.653	0.66±0.055	42±0.9
F9	454±0.8	3.7±0.952	0.79±0.052	45±1.2

All values are mean ± SD, n=3

Table No. 04: Physicochemical evaluation data of orodispersible tablets of Theophylline

Formulation code	Wetting time(sec)	Water absorption ratio	Invitro disintegration time(sec)	Drug content(%)
F1	69±0.35	81±0.96	40±1.5	90±0.63
F2	65±0.23	92±1.23	35±0.9	92±0.52
F3	52±0.12	98±0.54	30±0.5	99.5±0.23
F4	61±0.69	85±1.6	36±0.6	94±0.65
F5	59±0.52	91±2.1	42±0.7	100±0.59
F6	63±0.43	84±1.9	38±0.3	95.3±0.43
F7	58±0.65	96±0.45	39±0.9	89±0.49
F8	55±0.62	86±1.5	34±1.2	105±0.52
F9	63±0.56	89±2.2	32±1.4	98±0.68

All values are mean ± SD, n=3

Table No. 05: In vitro dissolution studies

Time (min)	Cumulative % drug dissolution								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
5	60.3	69.3	78.2	58.3	61.5	66.3	61.2	52.8	51.2
10	75.6	75.2	89.3	68.7	68.9	75.2	72.3	66.9	58.5
15	83.9	81.6	93.4	79.3	77.3	79.6	75.5	69.5	65.6
20	88.6	89.8	97.6	80.7	81.5	83.2	80.5	75.6	78.9
25	98.6	101.8	97.6	85.5	84.6	85.9	87.9	81.2	82.5
30	98.7	101.9	--	87.9	86.5	85.9	87.8	84.5	87.4

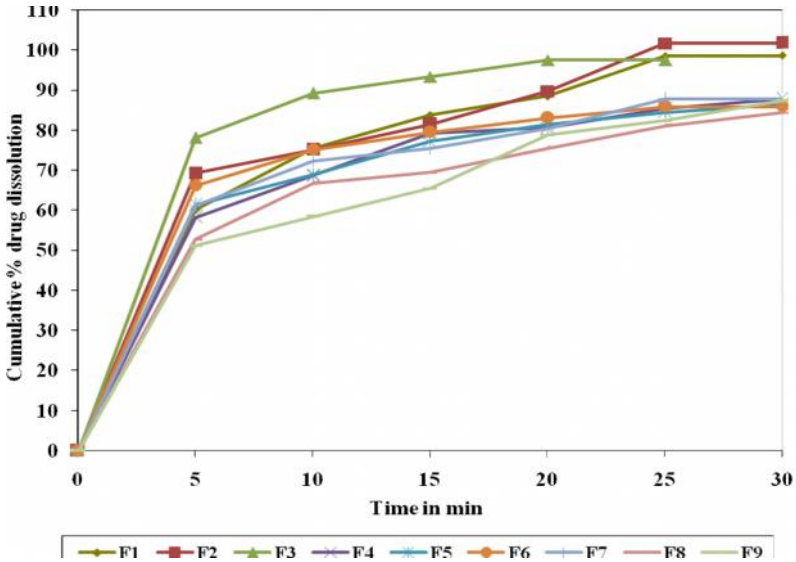

Fig. No. 04: Dissolution profile of formulations F1-F9

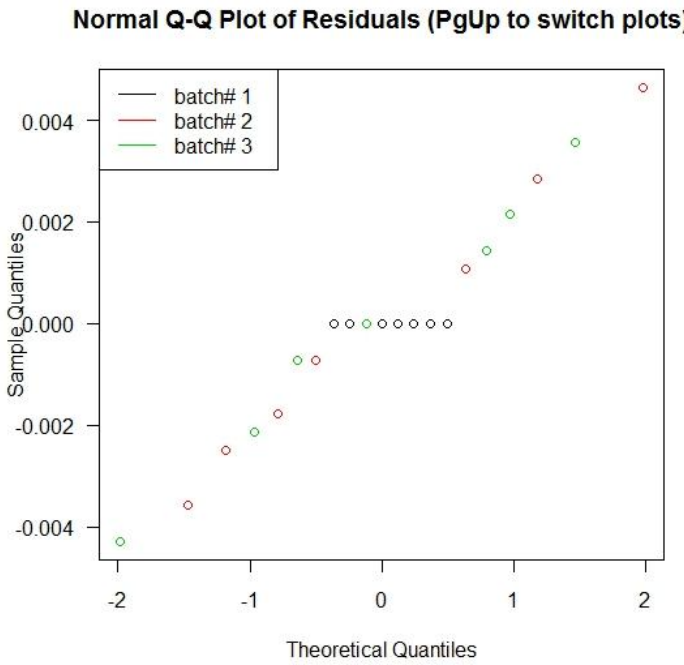

Fig. No. 05: Normal Q-Q plot of residuals obtained from calculated values of best formulation batches subjected for stability study

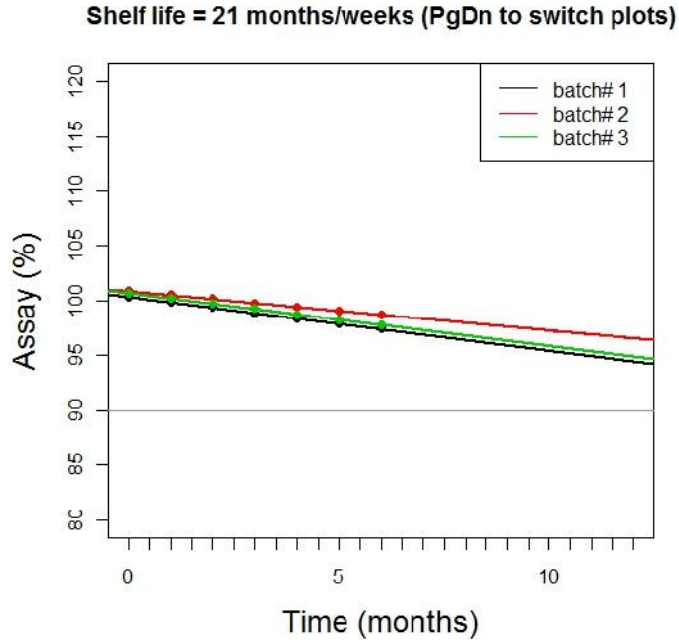

Fig. No. 06: Graph showing predicted shelf life of best formulation

Conclusion

From the above study, F3 formulation was selected as best formulation due to its less dispersion time and rapid dissolution of drug. The obtained results suggest that 120mg of crosspovidone is more suitable for the preparation of orodispersible tablets of Theophylline and shown better performance during the dispersion and dissolution. The bitter taste of the drug was masked by using required amount of sweetening agent. The mouth feel was also improved by using the suitable falvouring agents. Stability study reveals that F3 formulation is stable for the period of 21 months. It was concluded that the prepared orodispersible tablet formulation containing crosspovidone may fulfill the object of the present study.

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