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# Formulation Development and Evaluation of Saxagliptin as Mouth Dissolving Tablets

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**ABSTRACT:**

The objective is preparation and evaluation of mouth dissolving tablet for saxaglitin salt. Mouth Dissolving tablets of Saxagliptin hydrochoride were successfully formulated by employing direct compression method. Evaluation parameters like hardness and friability indicated good mechanical resistance of the tablets for all the formulations. Percentage weight variation and drug content uniformity were found to be within the approved range for all the formulations. The in-vitro release studies showed 78% of drug release in less than 5 minutes. Overall, in the formulations prepared by direct compression method, F8 which contain 15% CCS as Superdisintegrant releases 98.9 % drug in just 10 minutes was found to be best formulation. Taste masking has been done with Beta Cyclodextrin (1:1) ratio using kneading method. From the factorial batches. SXG8 gives faster release and Disintegration than the other formulation with optimum concentration of CCS. So SXG8 was optimized formulation having disintegration time is about 52 seconds. The stability studies carried out at 400C and 75 % RH for 1 month showed no significant change in drug content, In-vitro disintegration time and drug release profile revealing excellent stability of the formulated formulations.

**KEY WORDS:** Mouth Dissolving tablets, Saxagliptin, Beta Cyclodextrin, Taste masking agent, Croscarmellose sodium, Superdisintegrant.

## INTRODUCTION:

A Mouth dissolving drug delivery system, in most cases, is a tablet that dissolves or disintegrates in the oral cavity without the need of water or chewing these systems were first developed in the late 1970s for the people who experience difficulties in swallowing traditional oral solid-dosage forms with the concept to increase patient compliance. The novel technology of oral fast-dispersing dosage forms is known as fast dissolve, rapid dissolve, rapid melt and quick disintegrating tablets. It improves drug dissolution as well as onset of clinical effect and the pregastric absorption of drugs, which avoids first pass hepatic metabolism to reduce the dose than those observed from conventional dosage forms and finally, increase the bioavailability of drugs.

The Centre for Drug Evaluation and Research (CDER), US FDA defined Oral Disintegrating Tablets (ODT) as “A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.” MDTs disintegrate and/or dissolve instantaneously in the saliva without the use of water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the

rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely.

Drugs those disintegrate in mouth may absorb through either sublingual or buccal or gingival route or by all route. Selection of excipients and preparation techniques for preparation of Mouth dissolving tablets (MDT) are very important and this is dependant on physicochemical property of active drug substance. Present work has been done on mouth dissolving tablet of Saxagliptin Hydrochloride salt. Saxagliptin Hydrochloride is Dipeptidyl peptidase-4 inhibitor and its pharmacological action is as per below:

*Pharmacology*[1] **:** In humans, two incretin peptide hormones i.e. glucose-dependent insulinotropic polypeptide [GIP] and glucagon-like peptide-1 [GLP-1] have been identified. Incretin action facilitates the uptake of glucose by muscle tissue and the liver while simultaneously suppressing glucagon secretion by the α cells of the islets, leading to reduced endogenous production of glucose from hepatic sources.Both of these peptides are rapidly degraded by the enzyme DPP-4, which is expressed in a number of sites, including the endothelial cells of small gut arterioles.

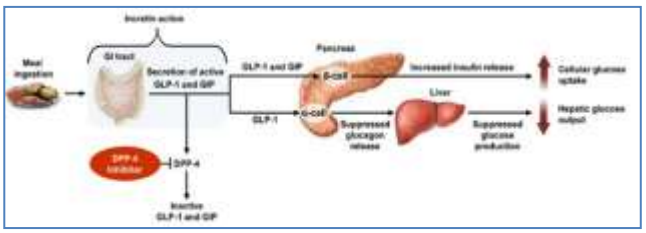


**Figure 1: Mechanism of *dipeptidyl peptidase-4 (DPP-4). The DPP-4 inhibitors prolong the action of endogenous incretins, enhancing the first-phase insulin response.***

**Advantage of MDT**[2,3]

- ✓ Ease of Administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as paediatric, geriatric & psychiatric patients.
- ✓ No need of water to swallow the dosage form, which is highly convenient feature for patients who are travelling and do not have immediate access to water.
- ✓ Good mouth feel property helps to change the perception of medication as bitter pill particularly in paediatric patient.
- ✓ Benefit of liquid medication in the form of solid preparation
- ✓ Pregastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects
- ✓ New business opportunities : product differentiation, line extension and life-cycle management, exclusivity of product promotion and patent life extension.
- ✓ The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety

**Disadvantage of drug delivery in MDT**[2,3]

- ✓ The tablets usually have insufficient mechanical strength i.e. hardeness. Hence, careful handling and packaging is required.
- ✓ For local action the rapid elimination of drugs due to the flushing action of saliva or the ingestion of foods stuffs may lead to the requirement for frequent dosing.
- ✓ The non-uniform distribution of drug within saliva on release from a solid or semisolid delivery system could mean that some areas of the oral cavity may not receive effective levels.
- ✓ For systemic delivery the relative impermeability of oral cavity mucosa with regard to drug absorption, especially for large hydrophilic biopharmaceuticals, is a major concern.

**MATERIAL AND METHOD**

**Material**[5,6,7] **:** Saxagliptin Hydrochloride, Sodium Starch Glycolate, Crospovidone, Croscarmellose Sodium, Microcrystalline Cellulose pH102, Citric Acid, Aspartame, Aerosil, Starcap 1500, Beta Cyclodextrin are provided by Aarti chemicals, Elite Pharmaceticals, Ratnamani chemicals.

**Method**

Saxagliptin Hydrochloride is slightly bitter in taste. So, Beta cyclodextrin is selected to use as taste masking agent. Solid dispersion of Saxagliptin hydrochloride with Beta cyalcodextrin is prepared. Beta cyalcodextrin is used as complexing agent to prepare solid dispersion of Saxagliptin hydrochloride by kneading methods using

drug: beta cyclodextrin in ratios 1:1 and 1:2 (Drug: Carrier). Methanol was selected as common solvent for of solid dispersions[52]. Then solid dispersion were mixed and blended with other excipients and then directly compressed into the tablet.

**Preparation of solid dispersion of Saxagliptin:** Accurately weighed amount of Saxagliptin Hydrochloride and β cyclodextrin were taken into glass mortar and then methanol was added in small quantity and the mixture was kneaded for 45 min and then dried in oven at 40 $^{o}$ C. The product obtained was pulverized and passed through mesh and stored in desiccator for further study[52]

**Preparation of Mouth dissolving tablet :**

- All the ingredients weight accurately as per formula.
- Sift all the material from 40 # sieve.
- The solid dispersion was mixed with proper portion of superdisintegrant.
- Care should be taken to confirm the proper mixing of drug and superdisintegrant.
- Then other excipients were added.
- Then the mixture is passed through sieve (Sieve No. 40 #).
- The mixture is blended with Aerosil ($SiO_2$).
- Finally the blend is subjected for compression using tablet punching machine.

**Formula Finalization** : Formulation Batches for mouth dissolving tablets of Saxagliptin prepared by using different types of Disintegrants. Mannitol is used as diluent cum sweetner. Aspartame used for giving sweetness to formulation and Aerosil used for flow improvement of blend. Citic acid is used as saliva stimulating agent as well as taste enhancer. Here Starcap 1500, Crospovidone and Croscarmellose sodium were evaluated for its suitability as superdisintegrant to get good direct compressible formulation. Starcap 1500 is used as disintergrant as well as dileunt. Table 1 gives the formulas of Saxagliptin β-CD Complex tablets.

**Table 1 Formulation table of Saxagliptin β-CD Complex tablets.**

| Ingredients (mg) | SXG1 | SXG2 | SXG3 | SXG4 | SXG5 | SXG6 | SXG7 | SXG8 | SXG9 |
|---|---|---|---|---|---|---|---|---|---|
| **Saxagliptin and β-CD Complex (1:1)** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Mannitol** | 35.4 | 32.4 | 29.4 | 35.4 | 32.4 | 29.4 | 35.4 | 32.4 | 29.4 |
| **Citric Acid** | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| **Sodium Starch Glycolate (SSG)** | 12 | 15 | 18 | - | - | - | - | - | - |
| **Crospovidone** | - | - | - | 12 | 15 | 18 | - | - | - |
| **Croscarmellose Sodium** | - | - | - | - | - | - | 12 | 15 | 18 |
| **Aspartame** | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| **Starcap 1500** | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 |
| **Aerosil** | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 |
| **Total weight (mg)** | **100.0** | **100.0** | **100.0** | **100.0** | **100.0** | **100.0** | **100.0** | **100.0** | **100.0** |

**Evaluation parameters**

**Evaluation of solid dispersion of Saxagliptin:**

**Drug Content:** Accurately weighed dispersion equivalent to 5 mg of Saxagliptin was transferred to 100 ml volumetric flask. Methanol was added up to the mark. After few minutes the solution was filtered; rejecting first few ml of the filtrate. 1 ml of filtrate was taken in a 10 ml volumetric flask and diluted up to the mark with Methanol to get 5 µg/ml concentration and then analyzed spectrophotometrically at 212 nm.

***In-vitro* dissolution studies:**

*In vitro* release studies were carried out using tablet USP type II dissolution test apparatus. Paddle speed was maintained at 75 rpm and 900 ml of pH 6.8 phosphate buffers was used as the dissolution medium. Samples (2 ml) were collected at predetermined time intervals and replaced with equal volume of fresh medium, filtered through a What man filter paper, and analyzed with a UV—Visible spectrophotometer at λ = 212 nm.

The preparation of tablets were evaluated for Pre-compression Parameters like Angle of Repose (θ), Bulk Density and Tapped Density, Compressibility index; and Post-Compression Parameters like Shape and colour of

tablets, Weight variation test, Uniformity of thickness, Hardness test, Friability test, Drug Content Uniformity, Wetting time, *In-vitro* dispersion time, *In-vitro* disintegration time and Drug Content.

**Drug Content Uniformity:** Five tablets were randomly selected, accurately weighed and average weight per tablet calculated. The tablets were ground individually to fine powder. Accurately weighed tablet powder, equivalent to 5 mg of Saxagliptin was transferred to 100 ml volumetric flask. Add methanol up to the mark. After few minutes the solution was filtered; rejecting first few ml of the filtrate. 1 ml of filtrate was taken in a 10 ml volumetric flask and diluted up to the mark with methanol and analyzed spectrophotometrically at 208 nm.

**Wetting time**[24]: A piece of tissue paper folded twice was placed in a Petri dish (internal diameter=9 cm) containing 10 ml of pH 6.8 phosphate buffer. A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting was recorded.

***In-vitro* dispersion time**[59]**:** It is determined by placing one tablet in a beaker containing 10 ml of pH 6.8 phosphate buffers at 37±0.5º C and the time required for complete dispersion was determined.

***In-vitro* disintegration time:**

The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration apparatus in pH 6.8 Phosphate buffer.

***In-vitro* dissolution studies:** *In vitro* release studies were carried out using tablet USP type II dissolution test apparatus. Paddle speed was maintained at 75 rpm and 900 ml of pH 6.8 phosphate buffers was used as the dissolution medium. Samples (2 ml) were collected at predetermined time intervals and replaced with equal volume of fresh medium, filtered through a What man filter paper, and analyzed with a UV—Visible spectrophotometer at λ = 212 nm.

**Drug Content**: All formulations were assessed for the drug content. A sample solution of concentration of 10 µg/ml had been prepared in methanol to determine the Assay using UV-spectrophotometer at λ = 212 nm.

**RESULT AND DISCUSSION**

**Determination of λmax and standard calibration curve of Saxagliptin**

A stock standard solution of 200 µg mL-1 was prepared by dissolving Saxagliptin in pH 6.8 phosphate buffer and methanol. Working standard solution was then prepared by suitable dilution of the standard stock solution with pH 6.8 phosphate buffer and methanol. The working standard solution was subjected to scanning between 200 to 400 nm and absorption maximum was determined . The λ max of saxagliptin was found as 212 nm given in figure 2 and 3.

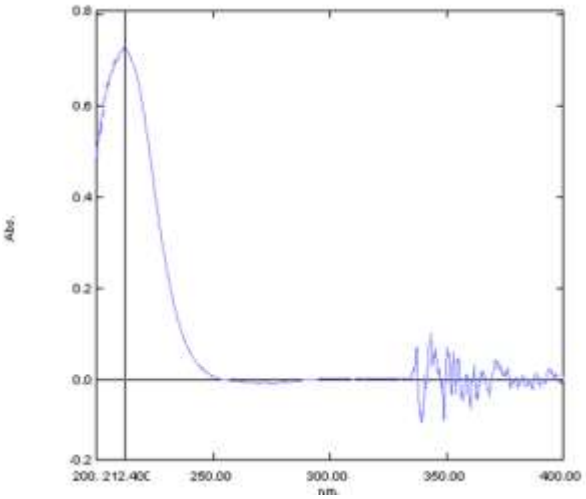



**Figure 2.:- Determination of λmax of Saxagliptin in pH 6.8 phosphate buffer**

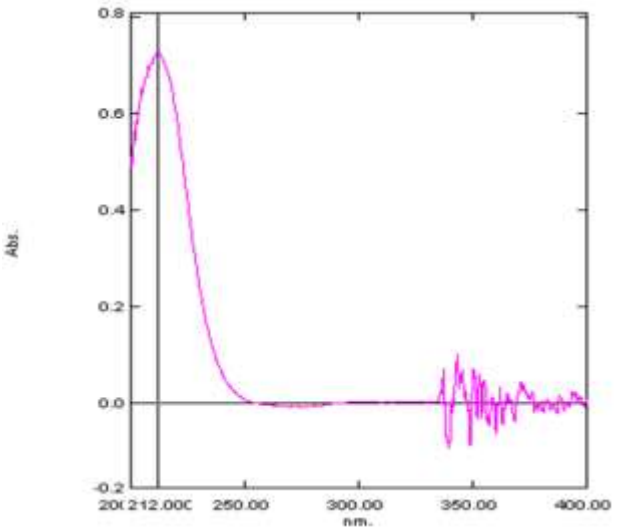



**Figure 3.:- Determination of λmax of Saxagliptin in methanol**

- ✓ The aliquots working standard solution was diluted se rially with sufficient phosphate buffer (pH 6.8) and

methanol to obtain the concentration range of 2-12 µg $ml^{-1}$.

✓ A calibration curves for Saxagliptin were obtained a s in below table 2 and 3

**Table 2 : Absorbance of Saxagliptin in in pH 6.8 phosphate buffer**

| Sr. No. | Concentration (µg/ml) | Absorbance Average ± SD |
|---|---|---|
| **1.** | 2 | 0.138 ± 0.003 |
| **2.** | 4 | 0.276 ± .002 |
| **3.** | 6 | 0.414 ± 0.003 |
| **4.** | 8 | 0.547 ± 0.002 |
| **5.** | 10 | 0.688 ± 0.003 |
| **6.** | 12 | 0.825 ± 0.003 |

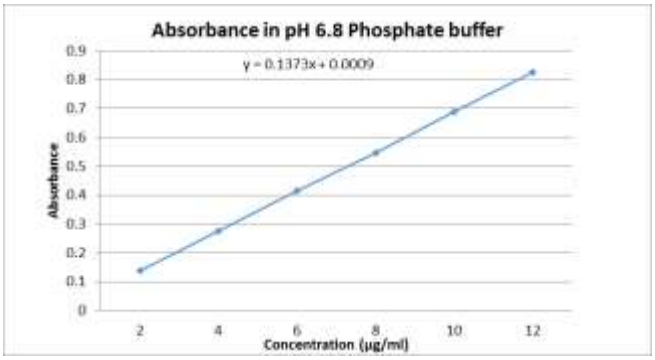



**Figure 4:- standard calibration curve of Saxagliptin in pH 6.8 phosphate buffer at 212 nm**

**Table 3 : Absorbance of Saxagliptin in methanol**

| Sr. No. | Concentration (µg/ml) | Absorbance Average ± SD |
|---|---|---|
| **1.** | 2 | 0.142 ± 0.003 |
| **2.** | 4 | 0.282 ± 0.002 |
| **3.** | 6 | 0.420 ± 0.004 |
| **4.** | 8 | 0.563 ± 0.002 |
| **5.** | 10 | 0.705 ± 0.003 |
| **6.** | 12 | 0.845 ± 0.003 |

**Evaluation of solid dispersion**

Prepared solid dispersion of drug analyzed for drug content and % drug release. Results were given in table 4 & 5; Based on result data of solid dispersion we concluded that 1:1 ratio was better than the 1:2 because it gives highest drug release in 20 min and drug content was also found more than remaining others.

Based on that 1:1 ratio was taken for further development.

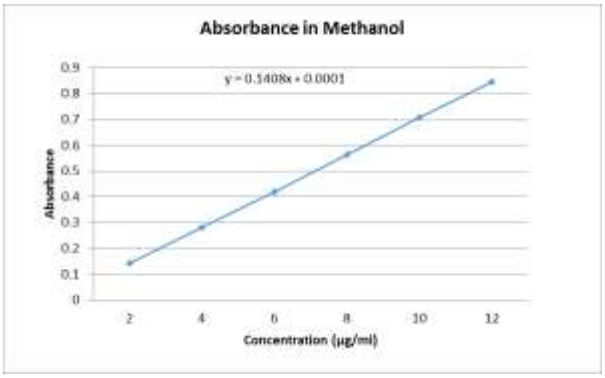



**Figure 5:- standard calibration curve of Saxagliptin in methanol at 212 nm**

**Table 4 : - Drug content of solid dispersion**

| Saxagliptin and β-CD Complex | Drug Content (%) |
|---|---|
| **1:1** | 97.8 ± 0.04 |
| **1:2** | 96.8 ± 0.08 |

**Table 5: - % Drug release of solid dispersion**

| Time in min | 1:1 | 1:2 |
|---|---|---|
| **5** | **57.6 ± 0.2** | 49.8 ± 0.4 |
| **10** | **71.8 ± 0.5** | 66.9 ± 0.5 |
| **15** | **88.9 ± 0.4** | 78.4 ± 0.7 |
| **20** | **99.7 ± 0.6** | 87.6 ± 0.9 |

**Pre compression parameters evaluation**

Pre compression parameters of SXG1-SXG9 batches were measured and results given in below table 6 From the results it concluded that all the batches have a good flow property and good for direct compression method.

**Table 6: Angle of Repose, Loose Bulk Density, Tapped Bulk Density and Carr's Compressibility Index**

| Formulations | Angle of Repose (θ) | Loose Bulk Density ($gm/cm^3$) | Tapped Bulk Density ($gm/cm^3$) | % Compressibility |
|---|---|---|---|---|
| **SXG1** | 26°56′ | 0.520 | 0.655 | 13.5 |
| **SXG2** | 27°72′ | 0.525 | 0.675 | 15.0 |
| **SXG3** | 25°60′ | 0.518 | 0.671 | 15.3 |
| **SXG4** | 28°10′ | 0.530 | 0.666 | 18.99 |
| **SXG5** | 29°38′ | 0.525 | 0.675 | 13.2 |
| **SXG6** | 27°48′ | 0.515 | 0.655 | 14.0 |
| **SXG7** | 25°89′ | 0.523 | 0.653 | 19.19 |
| **SXG8** | 26°32′ | 0.535 | 0.630 | 12.5 |
| **SXG9** | 30°12′ | 0.552 | 0.663 | 14.1 |

- **Post-compression parameters:**

The tablets prepared by direct compression technique were subjected to preliminary characterization such as hardness, thickness, % weight variation, friability and drug content. Details of results of post compression parameters of SXG1 - SXG9 given in below table 7

- ✓ Weight variation observed within a limit.
- ✓ All the formulation has a good hardness and because of good hardness also passed the friability test.
- ✓ Friability of all formulations found below 1 %.
- ✓ Thickness found within limit and no any variation found in formulation.

**Table 7: Uniformity of thickness, Hardness, Friability and Weight variation (SXG1-XG9)**

| Formulation Code | Uniformity of Thickness (mm) (n=10) | Hardness ($kg/cm^2$) (n=3) | Friability % | Weight Variation (mg) (n=10) |
|---|---|---|---|---|
| **SXG1** | 3.07 ± 0.02 | 3.40 ± 0.36 | 0.5 | 100 ± 2.36 |
| **SXG2** | 3.04 ± 0.03 | 3.76 ± 0.32 | 0.4 | 99 ± 2.36 |
| **SXG3** | 3.04 ± 0.02 | 3.86 ± 0.25 | 0.8 | 100 ± 2.05 |
| **SXG4** | 3.20 ± 0.06 | 3.67 ± 0.14 | 0.6 | 101 ± 2.78 |
| **SXG5** | 3.06 ± 0.08 | 3.96 ± 0.12 | 0.4 | 98 ± 2.72 |
| **SXG6** | 3.06 ± 0.03 | 3.84 ± 0.20 | 0.3 | 100 ± 2.46 |
| **SXG7** | 2.96 ± 0.03 | 3.77 ± 0.35 | 0.6 | 102 ± 2.30 |
| **SXG8** | 2.96 ± 0.01 | 3.54 ± 0.30 | 0.9 | 99 ± 2.10 |
| **SXG9** | 3.02 ± 0.05 | 3.88 ± 0.22 | 0.3 | 101 ± 2.01 |

**In-vitro disintegration time:**

The internal structure of tablets that is pore size distribution, water penetration into tablets and swelling of disintegration ingredients are suggested to be the mechanism of disintegration.

The results are shown in table 5, which was determined for all the developed formulations. Formulations SXG8 showed rapid disintegration compared to other formulations.

**In-vitro dispersion time:**

The in-vitro dispersion time is measured by the time taken to undergo uniform dispersion. Rapid dispersion within several minutes was observed in many formulations. The in-vitro dispersion data is tabulated in the table 5. Formulation F5 gave minimum In-vitro dispersion time i.e. 37 seconds.

**Wetting time:**

Wetting time is closely related to the inner structure of the tablet. The results of wetting time are shown in table 5, which showed that wetting process was very rapid in many formulations. This may be due to ability of swelling and also capacity of water absorption. Formulation F6 gave minimum wetting time i.e. 45 seconds.

**% Drug Content**

% Drug Content of SXG1 - SXG9 measured and found within limit. No any formulation deviates from the limit. Results were given in table 8.

**Table 8 : Evaluation of SXG1-SXG4**

| Formulation code | Wetting Time | *In-vitro* Dispersion Time | *In-vitro* Disintegration time | Drug Content |
|---|---|---|---|---|
| | (Seconds) | (Seconds) | (Seconds) | (%) |
| **SXG1** | 420 | 388 | 398 | 98.95 |
| **SXG2** | 303 | 249 | 311 | 97.91 |
| **SXG3** | 142 | 109 | 239 | 99.75 |
| **SXG4** | 86 | 64 | 99 | 98.66 |
| **SXG5** | 47 | 37 | 89 | 97.23 |
| **SXG6** | 45 | 42 | 80 | 101.5 |
| **SXG7** | 51 | 38 | 75 | 99.56 |
| **SXG8** | 59 | 48 | 52 | 99.9 |
| **SXG9** | 75 | 59 | 65 | 99.57 |

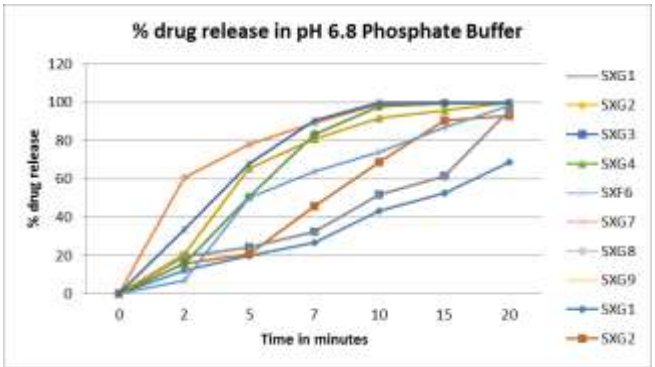
***In-vitro* dissolution studies:**

All the formulations were subjected for *in-vitro* dissolution studies using tablet dissolution apparatus. The dissolution medium 6.8 pH phosphate buffer was used to study the drug release.

The data obtained in the *in-vitro* release for formulations prepared by direct compression technique are shown in figure 6

All the formulations showed rapid % drug release. But the rapid drug dissolution was noticed in SXG8 formulation compared to other formulations which release 99.7 % drug in 2 minutes.

**Comparison of *In-vitro* Dissolution Profile of the Formulations (SXG1 - SXG9)**




## CONCLUSION

Mouth Dissolving tablets of Saxagliptin using its hydrochloride salt (i.e. Saxagliptin Hydrochloride) were successfully formulated by employing direct compression method and using β-cyclodextrin for taste masking.

- ✓ Evaluation parameters like hardness and friability indicated good mechanical resistance of the tablets for all the formulations. Also Percentage weight variation and drug content uniformity were found to be within the approved range for all the formulations.
- ✓ From the total study SXG8 has been selected as final formulation based on its overall behaviour in different tests. The *in-vitro* release studies showed 78 % of drug release in 5 minutes.
- ✓ Overall, the formulation batch SXG8 prepared by direct compression method, contains 15% CCS as Superdisintegrant releases which gives optimum drug release within 5 minuts.
- ✓ The selection of β-Cyclodextrin was done based on literature survey and ratio of Drug : β-Cyclodextrin was selected as (1:1) which was based on drug release study from the dispersion.
- ✓ So SXG8 was selected as target finalized formulation.

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