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Original Research Article

Formulation and Evaluation of Fast Dissolving Tablets of Sumatriptan Succinate

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ABSTRACT

Sumatriptan succinate (SUM) is potent and selective a 5-HT1D (5-hydroxy tryptamine 1D) receptor agonist used in the treatment of migraine and cluster headache. Sumatriptan Succinate undergoes extensive first pass metabolism with an oral bioavailability of approximately 15%. Hence the main objective of the study was to formulate fast dissolving tablets of sumatriptan succinate to achieve a better dissolution rate and further improving the bioavailability of the drug**.** Fast dissolving tablets of SUM were prepared by direct compression methods and blend was evaluated for the pre-compression parameters such as bulk density, compressibility, angle of repose etc. The tablets were prepared by using croscarmellose sodium, crospovidone and sodium starch glycolate as superdisintegrants in different concentration along with microcrystalline cellulose. Total six formulations were prepared and evaluated for hardness, friability, weight variation, content uniformity, wetting time, water absorption ratio, disintegration time and *invitro* drug release. *In-vitro* dissolution studies are performed by using phosphate buffer pH 6.8 at 75 rpm by paddle method. Overall, the formulation F4containing of croscarmellose sodium was found to be promising and has shown a disintegration time 45 sec. The stability studies were performed for two months (accelerated studies) as per ICH guidelines. The optimized formulation (F4) showed no significant variations for the tablets parameters and it was stable for the specified time period. Thus the results showed enhanced dissolution, which leads to improved bioavailability, improved effectiveness and hence better patient compliance.

Key words: Sumatriptan Succinate, Fast dissolving tablets, Direct compression, Superdisintegrants, Pre-compression.

INTRODUCTION

Due to increased life expectancy, the elderly constitutes a major portion of the world population today (Hisakadzu and Yunxia, 2002). Due to a decline in swallowing ability with age, a great many elderly patients complain that it is difficult for them to take some currently used dosage forms such as tablets, capsules or powders (Puttewar et al., 2010). Rapidly dissolving or quick dissolving dosage forms have acquired great importance in the pharmaceutical industry due to their unique properties and advantages

(Liang and Chen, 2001; Borsadia et al., 2003). Of all the dosage forms administered orally, the tablet is one of the most preferred dosage forms. Disintegrates are agents integrated to tablet and some encapsulated formulations to promote the breakup of the tablet and capsule slugs into more small fragments in an aqueous environment thereby incrementing the available surface area and promoting a more rapid release of the drug substance. They promote moisture penetration and dispersion of the tablet matrix. Tablet disintegration has received considerable attention as an essential step in obtaining fast drug release. The accentuation on the availability of drug highlights the importance of the relatively rapid disintegration of a tablet as a criterion for ascertaining uninhibited drug dissolution behavior. Number of factors affects the disintegration replace of tablets. The disintegrates have the major function to oppose the efficiency of the tablet binder and the physical forces that act under compression to compose the tablet. The stronger the binder, the more efficacious must be the disintegrating agents in order for the tablet to release its medication. Ideally, it should cause the tablet to disrupt, not only into the granules from which it was compressed, but additionally into powder particles from which the granulation was yare. Disintegrates are an essential component to tablet formulations. The ability to interact strongly with water is essential to disintegrate function. Combination of swelling and/or wicking and/or deformation is the mechanisms of disintegrant action. A disintegrant utilized in granulated formulation processes can be more efficacious if utilized both intragranularly and extragranularly thereby acting to break the tablet up into granules and having the granules further disintegrate to release the drug substance into solution. However, the portion of disintegrant integrated intragranularly (in wet granulation processes) is conventionally not as efficacious as that integrated extragranularly due to the fact that it is exposed to wetting and drying (as a component of the granulation process), which reduces the activity of the disintegrant. Since a compaction process does not involve its exposure to wetting and drying, the disintegrant used intragranularly inclines to retain good disintegration activity (Ansel et al., 1998; Jain and Sharma, 1998). Sumatriptan succinate is an agonist for 5-hydroxytryptamine receptors and it is widely prescribed for the treatment of migraine and cluster headaches. SUM undergoes an extensive biotransformation, mainly through Mono Amino Oxidase-A. It is a white to off line white powder bitter in taste and is readily soluble in water and in saline. The oral bioavailability of SUM is 14 ± 5 % owing to an important first pass metabolism. It has an elimination half-life of 2.5 hours and absorption zone from the upper intestinal tract. Plasma protein binding is low 14% to 21%. SUM 5-HT receptors (1D subtype) resulting in selective vasoconstriction of inflamed and dilated cranial blood vessels in the carotid circulation. It also blocks the release of vasoactive neuropeptides from perivascular trigeminal axons in the dura mater during migraine and may inhibit the release of inflammatory mediators from the trigeminal nerve (Marit and Gillian, 2006; Tripathi, 2008). Therefore, modified release type dosage forms would be useful to reduce dosing frequency and improve patient compliance. In present study an attempt has been made to formulate the orally disintegrating tablets by direct compression method using sodium starch glycolate, croscarmellose sodium and crospovidone as the superdisintegrants for rapid dissolution of drug and absorption, which may produce the rapid onset of action.

Materials and methods

Materials

Sumatriptan Succinate was a gift from Natco Pharma Ltd. (Hyderabad, India). Crospovidone, croscarmellose sodium and sodium starch glycolate was obtained from Hi-Media Laboratories Pvt. Ltd., Mumbai, India. Micro crystalline cellulose, mannitol, talc and

magnesium stearate was procured from Central Drug House (P) Ltd. New Delhi. All other solvents and chemicals used were of analytical grade.

Methods

Preformulation studies

Determination of λ_{max} of SUM

Accurately weighed 10 mg of drug was dissolved in 10 ml of phosphate buffer pH 6.8 solutions in 10 ml of volumetric flask. The resulted solution 1000µg/ml and from this solution 1 ml pipette out and transfer into 10 ml volumetric flask and volume make up with phosphate buffer pH 6.8 solution prepare suitable dilution to make it to a concentration range of 2-10µg/ml. The spectrum of this solution was run in 200-400 nm range in U.V. spectrophotometer (Labindia-3000+).

Preparation of tablets of SUM

Fast dissolving tablets of SUM were prepared by direct compression (Kuchekar et al., 2014) according to the formulae given in Table 1. All the ingredients were passed through # 60 mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 200 mg using 8 mm round flat punches on a Rimek mini press 16 station rotary compression machine.

Table 1 Composition of SUM fast dissolving tablets

Ingredients (mg)	Formulation code					
	F1	F2	F3	F4	F5	F6
Sumatriptan succinate	50	50	50	50	50	50
Sodium starch glycolate	15	30	-	-	-	-
Croscarmellose sodium	_	_	15	30	-	-
Crospovidone	-	-	-	-	15	30
Mannitol	10	10	10	10	10	10
Microcrystalline cellulose	114	99	114	99	114	99
Talc	5	5	5	5	5	5
Magnesium stearate	6	6	6	6	6	6
Total weight	200	200	200	200	200	200

Evaluation of fast dissolving tablets of SUM

Precompression parameters

Angle of repose (θ)

The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

$$\text{Tan } \theta = h/r$$

$$\theta = \tan\text{-}1\ (h/r)$$

Where, θ is the angle of repose, h is the height, r is the radius.

The granules were allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

LBD (Loose Bulk Density) = Mass of Powder/Volume of Packing

TBD (Tapped Bulk Density) = Mass of Powder/Tapped Volume of Packing

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index**.**

Carr's index (%) = [(TBD – LBD)/TBD] × 100.

Hausner's ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula (Subramanyam, 2001).

Hausner's ratio = Tapped density/Bulk density.

Evaluation of Tablets

Thickness

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital vernier caliper (Salsa et al., 1996).

Hardness

Tablet hardness was measured by using Pfizer hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations and results were expressed in Kg/cm^2.

Friability Test

From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, de dusted and reweighed. The friability was calculated as the percentage weight loss.

% friability was calculated as follows

$$\% \text{ Friability} = (W1 - W2) \times 100/W1$$

Where W1 = Initial weight of the 10 tablets, W2 = Final weight of the 10 tablets after testing.

Friability values below 0.5-1% are generally acceptable.

Weight variation test

To study weight variation individual weights (WI) of 20 tablets from each formulation were noted using electronic balance. Their average weight (WA) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

Drug content

The test is mandatory for tablets with 10 mg or less weight of active ingredient. Ten randomly selected tablets from each formulation (F1 to F6) were finely powdered and Drug equivalent to 10 mg of drug dissolved in 10 ml phosphate buffer pH 6.8 sonicate it for 20 minutes, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper No. 41. From this solution take 1 ml and diluted up to 100 ml with phosphate buffer pH 6.8 and the drug content was determined spectrophotometrically at 227 nm.

In vitro disintegration time

The disintegration test was performed using an USP disintegration apparatus, with distilled water at 24±0.50ºC. The time reported to obtain complete disintegration of six tablets were recorded and average was reported.

Dissolution rate studies

The prepared tablets were evaluated for *in vitro* drug release. The drug release studies were carried out using USP XXII paddle type Dissolution test apparatus. A tablet placed in dissolution media (900 ml) which was stirred at 75 rpm maintained at 37±0.2°C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 10ml Phosphate buffer pH 6.8. The samples withdrawn were assayed spectrophotometrically at 227 nm using UV visible spectrophotometer. The release of drug was calculated with the help of standard curve of PRE (Khan et al., 2019; Gautam et al., 2013).

Mathematical treatment of *in-vitro* release data

The quantitative analysis of the values obtained in dissolution/release tests is easier when mathematical formulas that express the dissolution results as a function of some of the dosage forms characteristics are used.

Zero-order kinetics

The pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged

action. The following relation can, in a simple way, express this model:

$$Q_t = Q_o + K_o t$$

Where Q_t is the amount of drug dissolved in time t, Q_o is the initial amount of drug in the solution (most times, Q_o=0) and K_o is the zero order release constant.

First-order kinetics

The following relation expresses this model:

$$\log Q_t = \log Q_o + \frac{K_1 t}{2.303}$$

Where Q_t is the amount of drug dissolved in time t, Q_o is the initial amount of drug in the solution and K_1 is the zero order release constant.

In this way a graphic of the decimal logarithm of the released amount of drug versus time will be linear. The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices, release drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminish.

Higuchi model

Higuchi developed several theoretical models to study the release of water-soluble and low soluble drugs in semi-solid and/or solid matrixes. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media.

The simplified Higuchi model is expressed as:

$$Q = K_H . t^{1/2}$$

Where Q is the amount of drug released in time t and K_H is the Higuchi dissolution constant. Higuchi model describes drug release as a diffusion process based in the Fick's law, square root time dependent. This relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms such as transdermal systems and matrix tablets with water-soluble drugs.

Korsmeyer-Peppas model

Korsmeyer *et al.* used a simple empirical equation to describe general solute release behaviour from controlled release polymer matrices:

$$\frac{M_t}{M_\infty} = a\, t^n$$

Where M_t/M_∞ is fraction of drug released, a is kinetic constant, t is release time and n is the diffusional exponent for drug release. 'n' is the slope value of log M_t/M_∞ versus log time curve. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. Peppas used this n value in order to characterize different release mechanisms, concluding for values for a slab, of n =0.5 for fickian diffusion and higher values of n, between 0.5 and 1.0, or n =1.0, for mass transfer following a non-fickian model. In case of a cylinder n =0.45 instead of 0.5, and 0.89 instead of 1.0. This equation can only be used in systems with a drug diffusion coefficient fairly concentration independent. To the determination of the exponent n the portion of the release curve where $M_t/M_\infty < 0.6$ should only be used. To use this equation it is also necessary that release occurs in a one-dimensional way and that the system width-thickness or length-thickness relation be at least 10. A modified form of this equation was developed to accommodate the lag time (l) in the beginning of the drug release from the pharmaceutical dosage form.

$$\frac{M_{t-l}}{M_\infty} = a\,(t - l)^n$$

When there is the possibility of a burst effect, b, this equation becomes:

$$\frac{M_t}{M_\infty} = at^n + b$$

In the absence of lag time or burst effect, l and b value would be zero and only at^n is used. This mathematical model, also known as Power Law, has been used very frequently to describe release from several different pharmaceutical modified

release dosage forms (Brahamankar and Jaiswal, 2009; Higuchi, 1963; Korsmeyer et al., 1983).

Results and Discussion

The λ_{max} of SUM was found to be 227 nm by using U.V. spectrophotometer (Labindia-3000+) in linearity range 2-10 µg/ml Fig.1. Tablet powder blend was subjected to various pre-compression parameters Table 2. The angle of repose values indicates that the powder blend has good flow properties. The bulk density, tapped density, compressibility index and Hauser's ratio of all the formulations was found to be within the range and showing that the powder has well flow properties. The results of post-compression parameters such as the uniformity of weight, hardness, thickness, friability and drug content of the tablets are given in Table 3. All the tablets of different batches complied with the official requirements of uniformity of weight. The hardness of the tablets ranged from 3.6 to3.9 kg/cm^2 and the friability values were less than 0.8% indicating that the tablets were compact and hard. The thickness of the tablets ranged from 2.2 to 2.4 mm. All the formulations satisfied the content of the drug as they contained 98.89 to 99.45 % of PRE and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practically within control. The result *in vitro* disintegration were within the prescribe limit and comply with the criteria for orally disintegrating tablets. The tablets were evaluated for *in vitro* dissolution studies in phosphate buffer pH 6.8 for 10 min. The results of the optimized formulation F4 showed maximum drug release i.e. 98.21 % at the end of 10 min. The results of release studies of formulations F4 was shown in Table 4. The *in vitro* drug release data of the optimized formulation F4 was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r^2' values of Korsmeyer's models was maximum i.e. 0.996 hence indicating drug release from formulations was found to follow Korsmeyer's models kinetics Table 5 & Fig. 2-5.

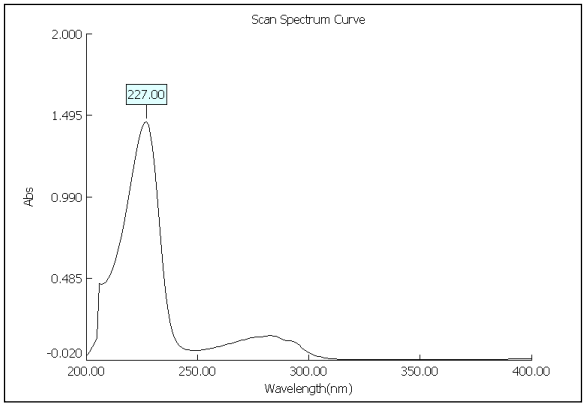


Figure 1 Determination of λ_{max} of SUM

Table 2 Results of pre-compression parameters of SUM

Formulation code	Parameters			
	Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	0.325	0.426	23.709	1.311
F2	0.335	0.448	25.223	1.337
F3	0.326	0.431	24.362	1.322
F4	0.328	0.429	23.543	1.308
F5	0.329	0.432	23.843	1.313
F6	0.331	0.432	23.380	1.305

Table 3 Results of post-compression parameters of all formulations

F. Code	Hardness test (kg/cm^2)*	Friability (%)*	Weight variation (%)*	Thickness (mm)*	Drug content (%)*	Disintegration Time (sec.)* Mean ± SD
F1	3.8	0.785	200	2.3	98.89	65
F2	3.9	0.658	205	2.2	99.12	80
F3	3.8	0.789	206	2.4	98.98	72
F4	3.7	0.658	198	2.4	99.45	45
F5	3.6	0.754	196	2.3	98.98	62
F6	3.7	0.658	204	2.4	99.32	32

***Average of three determinations (n=3)**

Table 4 *In-vitro* drug release data for optimized formulation F4

Time (min)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
2	1.414	0.301	45.23	1.655	54.77	1.739
5	2.236	0.699	73.32	1.865	26.68	1.426
10	3.162	1	98.21	1.992	1.79	0.253

Table 5 Regression analysis data

Batch	Zero Order	First Order	Higuchi	Korsmeyer-Peppas
	R^2	R^2	R^2	R^2
F4	0.968	0.968	0.995	0.996

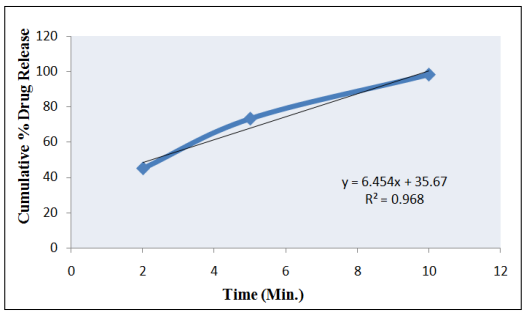


Figure 2 Zero orer release Kinetics

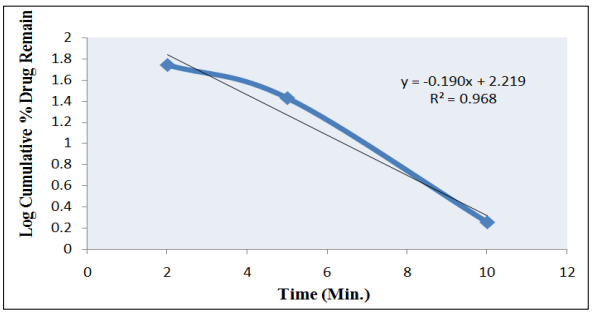
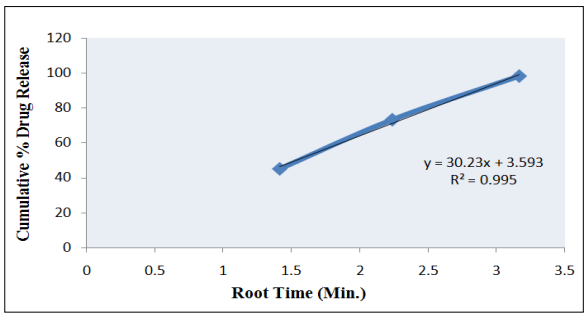


Figure 3 First order release kinetics



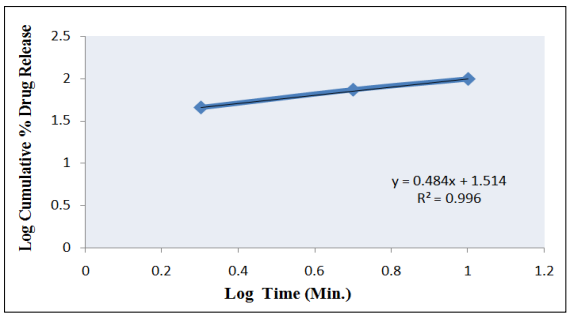


Figure 4 Higuchi release kinetics

Figure 5 Korsmeyer-Peppas release kinetics

Conclusion

Thus from the whole research work it can be concluded that, the oral fast dissolving tablet of SUM were formulated and evaluated for various parameters. All evaluation parameter were within specification. The croscarmellose sodium shown faster drug release than sodium starch glycolate and crospovidone. Formulation F4 release maximum drug within the 10mins.ie. 98.21 % and shown minimum disintegration time i.e. 45sec than other formulation and hence considered best formulation.

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