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Application of Ion Exchange Resin in the Formulation and Development of Repaglinide Mouth Dissolving Tablets

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ABSTRACT

Mouth dissolving tablets are gaining more demand and popularity from last few years since these dosage forms when placed in the mouth disperse readily in the saliva and thus make it easy to swallow for geriatric and pediatric patients. This experimental study was performed to formulate and develop Repaglinide mouth dissolving tablet which shall be helpful for these patients and shall increase the patient compliance. Polacrilin Potassium was be used as a super disintegrant that was found better as compared to Croscarmellose sodium in the development of Mouth dissolving tablet of Repaglinide because of their smaller particle size, the high rate of swelling. Moreover, colloidal silicon dioxide when used intragranularly makes the granules more porous for water penetration and acted as an effective disintegrant for the tablet. A quantity of Poloxamer as surfactant/solubilizing agent, Polacrilin potassium as the disintegrant and Magnesium stearate as lubricant plays an important role in the performance of Repaglinide mouth dissolving tablets. 4% w/w of Polacrilin potassium, 0.3%w/w of Poloxamer 188 and 0.7% w/w of magnesium stearate were found to be the optimum concentrations (F6) for the formulation of Repaglinide mouth dissolving tablets.

INTRODUCTION:

The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness. However geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance[1].Recently pharmaceutical industry has become increasingly aware of the need that elderly be considered as a separate and unique Medicare population. Though geriatric patients constitute a minor proportion of the population, its growth rate is high hence will have the significant impact on the development of drug delivery systems [2]. Thus mouth dissolving tablets are gaining more demand and popularity from last few years. Traditional tablets and capsules administered with 250 ml of water may be inconvenient or impractical for geriatric and pediatric patients. Hence mouth dissolving tablets are a perfect fit for them. Mouth dissolving tablets dissolve or more commonly disintegrate rapidly in the saliva without the aid of water. These dosage forms are placed in the mouth, allowed to disperse in the saliva, to produce a suspension which can be easily swallowed by the patient. The advantage of this convenient administration has encouraged both academic and industry to generate new fast disintegrating formulations. Less frequently, they are designed to be absorbed through the buccal and oesophageal mucosa as the saliva passes through the stomach. In the latter case, the bioavailability of a drug from mouth dissolving tablets may be even greater than that observed for standard dosage forms [3,4].

Diabetes is a most prevailing disease in geriatrics and these patients feel difficulties in swallowing anti-diabetic drug. In market Repaglinide tablet which is an anti-diabetic drug is available as 0.5 mg, 1 mg, and 2 mg as a film-coated tablet. But there is no mouth dissolving tablets available in the market. So the objective of this experimental study is to formulate and develop Repaglinide mouth dissolving tablet dosage form that shall be helpful for these patients and shall increase the patient compliance.

Ion exchange resin can be used as an effective disintegrant in the formulation of mouth dissolving tablets. Resins although insoluble, have the great affinity for water and hence, act as a disintegrant. Moreover, because of their smaller particle size, the rate of swelling is high making them super disintegrant. Like conventional disintegrant, they don't lump but additionally, impart strength to the tablets[5]. Potential super disintegrant ability of Indion® 414 has been reported for mouth dissolve tablets of Roxithromycin, Montelukast sodium and

Dicyclomine hydrochloride [6]. So Polacrilin potassium (Tulsion T-339) is chosen as a suitable disintegrant for this experimental study for achieving DT less than 30 sec.

The patent information was collected from an orange book of USFDA and found that patent on innovator product has expired and there is no unexpired patent related to an innovator. Innovator sells Repaglinide film-coated tablets as brand name PRANDIN[7].

Neither Mouth dissolving tablet nor plain film-coated tablet is official in Indian Pharmacopeia (IP).However, Repaglinide tablet is official in USP. So USP method of Dissolution is taken for the analysis of developed product to check its performance as compared to Reference marketed product.

MATERIALS AND METHODS:

MATERIALS:

Repaglinide was obtained from M/s Torrent Pharmaceuticals Pvt. Ltd., Ahmedabad, India. Polacrilin Potassium resin (Tulsion T339) was obtained as a gift sample from Thermax Ltd., Pune, India.

METHODS:

1. Procurement of market product (reference standard) and its characterization

100 (1X10) tablets of Repaglinide 2mg (Eurepa 2mg) were procured from the market. Market Tablets were tested for average weight, tablet shape (Diameter and thickness), hardness, disintegration time and dissolution. Average weight was calculated by taking the individual tablet weight in analytical balance. Tablet diameter and thickness were measured by using Vernier caliper. Hardness was measured by using Monsanto hardness tester. Six tablets were taken in Disintegration apparatus and disintegration time was checked at 37±2°C without a disk. Dissolution was performed as per the procedure mentioned in United State Pharmacopoeia (USP) for Repaglinide tablets.

2. Selection of Excipients for formulation of Mouth dissolving tablets and Drug-excipients compatibility study

Since contributing to the major portion of formulation, excipients shall be selected in such a way that it shall not only increase the bulk of tablet but also have the property of being

stable/compatible with API, should have its own compressibility and should be soluble in case of formulation having poorly soluble drug such as Repaglinide. For the formulation of Repaglinide mouth dissolving tablets, same excipients that are used in innovator product Prandin were selected. Because same excipients are already proved to be compatible and stable with API. Prandin contains the inactive ingredients such as calcium hydrogen phosphate (anhydrous), microcrystalline cellulose, maize starch, Polacrilin potassium, Povidone, glycerol (85%), magnesium stearate, Meglumine, and Poloxamer[8].Since these excipients are for film-coated tablets, not for mouth dissolving tablet, some other excipients croscarmellose sodium, lactose, Mannitol (Pearlitol SD200), colloidal silicon dioxide are also taken into consideration for formulation and development.

The drug was mixed with above excipients along a particular ratio mentioned in table-1 and kept vials in duplicate. Vials of a 1st set were closed with rubber closure and sealed and kept in an oven at 60±5°C kept for 3 weeks. Similarly, 2nd set was closed with rubber closure that is punctured with a needle to make it permeable to external temperature and humidity and kept in ambient environmental condition for 3 weeks. At the end of each week, samples were checked visually for any color change by comparing with the control sample of only API and mixture of all excipients kept in two separate vials at the sealed condition.

Table 1: Drug-excipients compatibility study

Excipients (E)	Drug: Excipient	Vial with punctured rubber closure/cap at ambient environmental condition			Sealed vial kept at 60°C in oven		
		1 week	2 week	3 week	1 week	2 week	3 week
Calcium hydrogen phosphate	1:10	No change	No change	No change	No change	No change	No change
Microcrystalline cellulose (PH101)	1:10	No change	No change	No change	No change	No change	No change
Maize Starch	1:10	No change	No change	No change	No change	No change	No change
Polacrilin potassium	1:5	No change	No change	No change	No change	No change	No change
Povidone (k-30)	1:5	No change	No change	No change	No change	No change	No change
Glycerol (87%)	1:5	No change	No change	No change	No change	No change	No change
Magnesium stearate	1:1	No change	No change	No change	No change	No change	No change
Meglumine	1:5	No change	No change	No change	No change	No change	No change
Poloxamer 188	1:5	No change	No change	No change	No change	No change	No change
Mannitol	1:10	No change	No change	No change	No change	No change	No change
Croscarmellose sodium	1:5	No change	No change	No change	No change	No change	No change
Colloidal silicon dioxide	1:5	No change	No change	No change	No change	No change	No change

3. Formulation and optimization of Repaglinide mouth dissolving tablets 2 mg

Wet granulation method was selected for the formulation of mouth dissolving tablets since innovator also used the same method as evident from the presence of liquid excipients such as Poloxamer and Glycerol 85%. A moreover Dry mix of Drug, Anhydrous Calcium Hydrogen phosphate, mannitol, microcrystalline cellulose Starch was checked for flow

property by calculating Compressibility index, an angle of repose using Funnel method and concluded the dry mix having poor flow and poor compressibility. The limit of disintegration time (DT) for mouth dissolving tablet is NMT 30 second. Since the market product is a film-coated tablet, it has a DT of 59 seconds. To make the tablet disintegrate within 30 seconds, it was decided to keep the tablet average weight less than the market product (i.e. 100mg) and shape as round, so that tablet will take less time to disintegrate.

Total eleven type of formulation (F1 to F11) of Repaglinide mouth dissolving tablets 2mg with batch size 500 tablets (50gm) were prepared as per below manufacturing procedure using the formula mentioned in table-3.

- Binder preparation: Required quantity of Meglumine, Poloxamer 188, Povidone K-25 and Glycerol 87% were mixed with 20ml of purified water to form a clear solution.

- Dry mixing: Required quantity of Repaglinide was mixed geometrically with an intragranular material in the polythene bag and passed through the 40# sieve. Then it was mixed properly in the polythene bag for 5 minutes.

- Granulation: Above drymix, material was granulated with binder solution and wet milling was done through 12# sieve.

- Drying: The wet milled material was then dried in hot air oven at 50±5°C till the LOD (Loss on drying) of the granule reaches below 2%.

- Sizing of granules: Dried granules were sifted through the 40# sieve.

- Blending and Lubrication: Required quantity of blending material was sifted through 40# and mixed properly with dried milled granule in the polythene bag for 5 min.

- Lubrication: Required quantity of magnesium stearate was sifted through 60# and mixed with an above-blended material in the polythene bag for 3min.

- Compression: Lubricated blend were compressed with 7.10 mm, round, concave, B tooling punches and dies using manual tablet compression machine with following compression parameters.

Average weight -100 mg ± 5% (95-105mg)

Uniformity of Weight-100 mg ± 7.5% (92.7-107.5mg) (limit as per IP)

Hardness-2-3 Kg/cm^2

Friability- NMT 1.0% w/w (limit as per IP)

4. Optimization of a quantity of surfactant/solubilizing agent (Poloxamer 188), the disintegrating agent (Polacrilin Potassium) and lubricant (Magnesium stearate) :

Optimization of Surfactant/Solubilizing agent concentration helps in overcoming problems associated with poor dissolution performance of the product. Poloxamer was evaluated in concentration 0.15%, 0.3% and 0.6% w/w in formulation F5, F6 and F7 respectively.Polacrilin Potassium was evaluated in concentration 2.00%, 4.00% and 6.00% w/w in formulation F5, F10 and F11 respectively. Optimization of Lubricant concentration help in overcoming the problem associated with poor DT and dissolution performance of the product and tablet properties. Magnesium stearate was evaluated in concentration 0.35%, 0.70% and 1.40% w/w in formulation F5, F8 and F9 respectively.

5.Characterization of Mouth Dissolving Tablet

5.1 Uniformity of weight and Average weight of Tablet:

20 tablets were placed in analytical weighing balance and weight was recorded. Average weight was calculated by dividing total weight by the number of tablets. Uniformity of weight was calculated by placing 20 Tablets on analytical weighing balance one by one to check the individual tablet weight. Uniformity of weight was calculated by using following formula,

$$+ve\ \%\ weight = \frac{(Maximum\ tablet\ weight - Average\ tablet\ weight)}{Average\ tablet\ weight} \times 100$$

$$-ve\ \%\ weight = \frac{(Minimum\ tablet\ weight - Average\ tablet\ weight)}{Average\ tablet\ weight} \times 100$$

Since average weight Repaglinide was kept 100mg so individual tablet weight was kept as per the limit mentioned in Indian Pharmacopeia (IP) i.e. within 100 ±7.5% (92.5 mg t0 107.5mg).

5.2 A hardness of Tablet:

Tablet was put in Monsanto hardness tester and amount of force required to break the tablet was noted.

5.3 Thickness and Diameter of tablets:

Vernier caliper was used to measure thickness and diameter of a tablet in millimeter (mm).

5.4 Friability of Tablets:

Friability was tested to check the ability of the tablet to resist the abrasion during handling and transport. It was tested as per procedure laid in Indian Pharmacopeia (IP). Tablets equivalent to 6.5 gm or 10 tablets (whichever is more) were weighed and placed in Roche friabilator and run for 4 minutes at 25 rpm. Final weight was noted and friability was calculated in percentage by using following formula

$$\text{Friability (\%)} = \frac{\text{(Initial weight-final weight)}}{\text{(Initial weight)}} \times 100$$

Friability (%) of mouth dissolving tablets should not be more than 1.0% w/w as per limit mentioned in IP.

5.5 Disintegration Test (DT):

The disintegration of the tablet was tested as per the procedure mentioned in IP by placing 6 tablets, one in each tube of Disintegration apparatus with 800ml purified water (Temperature 37±2°C).The time required to disintegrate with no mass remaining in all six tubes was noted. DT mouth dissolving tablet should not be more than 30 seconds.

5.6 Dissolution

Method of performing dissolution was kept in line with procedure mentioned in USP as given below,

Dissolution Medium: pH 5.0 citrate buffer

Quantity of Medium taken: 900 mL

Type of Dissolution Apparatus: Paddle

RPM of Paddle: 75 rpm

Time: 30 and 45 min.

Tolerances: NLT 70% (Q) of the labeled amount of Repaglinide is dissolved

Citrate buffer pH5 was prepared by mixing 10.2 g of citric acid monohydrate and 18.16 g of dibasic sodium phosphate dihydrate with 1 L of water. The dosage form was placed in the Dissolution bowl with 900ml medium. Dissolution was run at 75 rpm. After 30 min, 10ml of a solution was withdrawn and filtered through Whatman filter paper. The filtrate was then analyzed by taking the absorbance of solutions at λmax 241.1nm using UV double beam spectrophotometer and put on the standard calibration curve of step 3.4.3 (calibration curve in citrate buffer pH5) to get the amount of drug dissolved in 30 min (% Dissolution).

RESULTS AND DISCUSSION:

1. Procurement of market product (reference standard) and its characterization

10X10 tablets were procured from the market. These tables shall be considered as standard since it is approved by the regulatory body with the proof that it is bioequivalent against innovator product. Tablet average weight was found to be 113.0 mg (108 to 119 mg). Eurepa tablet is round tablet with one side scored and plain on another side with a diameter of 6.30 mm and thickness of 2.0 to 2.15 mm. Hardness was measured with Monsanto Hardness tester and found to be 3 to 5 Kg/cm^2.

Six tablets were taken in Disintegration apparatus and Disintegration was checked at 37±2° C without a disc. Disintegration time was found to be 1 min 59 seconds. Dissolution was performed as per the procedure mentioned in step 5.6 and presented in table-2.

Table 2: Dissolution of market product

Dosage unit	% Dissolution in 30 min
tab 1	87
tab 2	89
tab 3	88
tab 4	89
tab 5	87
tab 6	84
mean	87.20
RSD	2.22

The limit of disintegration time (DT) for mouth dissolving tablet is NMT 30 second. Since the market product is a film-coated tablet, it has a DT of 1 minute 59 second. To make the tablet disintegrate within 30 seconds, the tablet average weight was kept minimum (i.e.100mg) and shape as round, so that shape and size of tablet will be comparatively smaller than market product and will take less time to disintegrate.

2. Selection of Excipients for formulation of Mouth dissolving tablets and Drug-excipients compatibility study

Since no color change observed after 3 weeks of storage at 60±5°C and also under exposure to ambient temperature and humidity in comparison to control sample of API, so all the excipients were found compatible with the drug.

3. Formulation and optimization of Repaglinide mouth dissolving tablets 2 mg

Repaglinide mouth dissolving tablets 2mg was prepared by wet granulation method as described previously. Only Disintegration and Dissolution was performed as per the standard testing procedure of step 5.5 and 5.6 during optimization of formulation because these are the most important critical quality attribute that quantifies the similarity of a performance of a developed product and Market product.

Table 3: Formulation of repaglinide mouth dissolving tablets 2 mg

Batch No.		**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**
Intra-granular	**Formulation(mg/Tablet)**											
	Repaglinide	2	2	2	2	2	2	2	2	2	2	2
	Calcium hydrogen phosphate	40.3	40.3	33.8	33.8	33.8	33.8	33.8	33.8	33.8	33.8	33.8
	Mannitol (Pearlitol SD200)	0	10	23	23	23	23	23	23	23	23	23
	MCC(PH 101)	37.3	37.	30.	30.	30.	30.	30.	31.	30	32.	28.
	Maize Starch	10	X	X	X	X	X	X	X	X	X	X
	Color Quinoline	0.05	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Colloidal silicon Dioxide	X	X	X	X	1.4	1.4	1.4	1.4	1.4	1.4	1.4
Binder	Meglumine	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
	Poloxamer 188	0.15	0.1	0.1	0.1	0.1	0.3	0.6	0.3	0.3	0.3	0.3
	Povidone (K-25)	2	2	2	2	2	2	2	2	2	2	2
	Glycerol 87%	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
	Purified water	0	0	0	0	0	0	0	0	0	0	0
Extra-granular	Polacrillin potassium (TulsionT339)	X	X	X	4	4	4	4	4	4	2	6
	Crosscarmellose sodium	4	4	4	X	X	X	X	X	X	X	X
	Colloidal silicon dioxide	1.4	1.4	1.4	1.4	X	X	X	X	X	X	X
	Aspartame	0.05	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Flavour orange dry	0.05	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Magnesium stearate	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.3	1.4	0.7	0.7
	Tablet weight (mg)	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100#**	**100**	**100**	**100**
DT	Market tablet 1 min 59 sec	1min 35sec	1min 12sec	59 sec	38 sec	25 sec	23 sec	26 sec	22 sec	42 sec	49 sec	20 sec
% Disso	87.2	Not performed				81.70	90.4	91.0	Not performed			89.6

Tablet sticking observed

A prototype formulation (F1) was prepared using the same excipients (as used by innovator) and quantity was initially taken based on prior knowledge and product understanding. Disintegration time was found more as compared to market product and also didn't meet the DT criteria of Mouth dissolving tablets (i.e. DT being NMT 30 second). So to decrease the disintegration time, water-soluble excipient like Mannitol (Pearlitol SD200) was used replacing maize starch (formulation F2) and found that DT decreased by 23 seconds. Due to the advantage of mannitol observed in disintegration time, Mannitol quantity was increased to 24.4 mg/tablet by adjusting the quantity of Anhydrous Calcium hydrogen phosphate and MCC (PH101) by almost equal proportion in formulation F3.DT was improved to 59 seconds.

As a mouth dissolving tablet, DT should be less than 30 seconds. In order to decrease the DT further, Croscarmellose was replaced in formulation F4, with the same quantity of Polacrilin Potassium (Tulsion-339), which is known for its unusually large swelling property. Like conventional disintegrant, they don't lump but additionally, impart strength to the tablets which are evident from increased hardness in this batch. DT decreased to 38 seconds. Still, DT was found more than 30 seconds.

In formulation F5, 1.4% of Colloidal silicon dioxide was used intragranularly and DT found to be below 30 seconds. It was due to colloidal silicon dioxide when used intragranularly, make the granules more porous for water penetration.

Dissolution was not performed for Formulation F1, F2, F3 and F4 since these formulations did not meet the criteria of Mouth dissolving tablet for DT being within 30second. Formulation F5 was the developed formulation that passes all the criteria for being Mouth dissolving tablets. So tablets of this batch were tested for Dissolution as per the method mentioned in step 5.6 to check its performance in drug release with respect to market product and found that it has less drug release (i.e. 81.7%) with respect to the market product. However, it passes the dissolution acceptance criteria of USP (i.e. 75% in 30 min).

A function of each ingredient was highlighted below, out of which quantity of Poloxamer as surfactant/solubilizing agent, Polacrilin potassium as the disintegrant and Magnesium stearate as lubricant play important role in the performance of the developed product and hence need to be optimized.

4. Optimization of a quantity of surfactant/solubilizing agent (Poloxamer 188), the disintegrating agent (Polacrilin Potassium) and lubricant (Magnesium stearate) :

It was observed from the dissolution data that, the batch made with 0.3% Poloxamer (F6) and 0.6 % (F7) Poloxamer showed no significant difference in dissolution, drug release being 90.4 and 91.0% respectively. However, there is no effect of Poloxamer concentration on the change in DT. The batch with 0.3% Poloxamer 188 (F6) was chosen for further optimization since it showed better drug release as compared to formulation with 0.15% Poloxamer (F5).

It was observed from the dissolution data that, the batch made with 4.00% Polacrilin Potassium (F6) and 6.00 % Polacrilin Potassium (F11) showed no significant difference in dissolution, drug release being 90.4 and 89.6% respectively. Batch made with 2% Polacrilin Potassium fails in DT and hence dissolution was not carried out. The batch with 4.00% Polacrilin Potassium was chosen for further optimization.

It was observed from the dissolution data that, the batch made with 0.35% Magnesium stearate (F8) and 0.70% Magnesium stearate (F6) showed similar disintegration time. But batch made with 0.35% Magnesium stearate showed tablet sticking problem and not considered as optimized concentration and hence, not tested for dissolution.

Batch made with 1.4% Magnesium stearate (F9) fails in DT and hence Dissolution profiling was not carried out. Thus increased magnesium stearate affects the disintegration of tablets. So the batch with 0.70% Magnesium stearate was chosen for further optimization.

CONCLUSION:

Polacrilin Potassium can be used as a better super disintegrant as compared to Croscarmellose sodium in the development of mouth dissolving tablet of Repaglinide. Moreover, colloidal silicon dioxide when used intragranularly makes the granules more porous for water penetration and can act as an effective disintegrant for the tablet. Repaglinide being poorly soluble compound need the support of surface active/solubilizing agent like Poloxamer 188 to get dissolved rapidly in the gastric environment. Increase in concentration of Poloxamer 188 increased the dissolution of Tablets.

Quantity of Poloxamer as surfactant/solubilizing agent, Polacrilin potassium as disintegrant and Magnesium stearate as lubricant play important role in the performance of Repaglinide

Mouth dissolving tablets.4% w/w of Polacrilin potassium, 0.3%w/w of Poloxamer 188 and 0.7% w/w of magnesium stearate was found to be the optimum concentrations (F6) for the formulation of Repaglinide mouth dissolving tablets.

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REFERENCES:

1. Basu B, Bagadiya A, Makwana S, Vora V, Batt D, Dharamsi A. Formulation and evaluation of fast dissolving tablets of cinnarizine using superdisintegrant blends and subliming material. Journal of Advanced Pharmaceutical Technology and Research. 2011; 2: 266–273.
2. Yellanki SK.Design and *in-vitro* evaluation of orally disintegrating tablets of Selegiline. International Journal of Current Pharmaceutical Research. 2015; 7:37-39.
3. Seager H. Drug delivery products and the Zydis fast-dissolving dosage form. Journal of Pharmacy and Pharmacology. 1998; 50: 375–382.
4. Yarwood R. Zydis a novel fast dissolving dosage form for man. Chem. 1990; 36–37.
5. Mahore JG, Wadher KJ, Umekar MJ, Bhoyar PK. Ion Exchange Resin: Pharmaceutical application and recent advancement. International Journal of Pharmaceutical Sciences Review and Research. 2010; 1(2): 8-13.
6. Amin P, Prabhu N, Wadhwan A.Indian 414 as Superdisintegrant in Formulation of Mouth Dissolve Tablets.Indian J Pharm Sci. 2006; 68: 117-11.
7. FDA U.S. Food and Drug Administration. Orange book: Approved drug products with therapeutic Equivalence Evaluations. 12/15/2017.
https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=020741 (15/12/2017).
8. RxList. Prandin. 3/13/2017. https://www.rxlist.com/prandin-drug.htm (15/12/2017).